

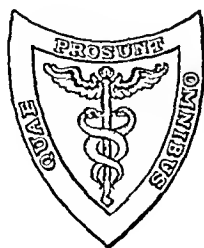
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ORIGINAL ARTICLES.

**BASOPHILIC HYPERPLASIA OF THE PITUITARY IN
ESSENTIAL HYPERTENSION.**

By IRVING PARDEE, M.D.,

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HYPERTENSION unassociated with renal disease or serious arterial change has been long the object of etiologic debate. There is growing evidence to demonstrate a close relationship between the endocrine glands and this form of hypertension. A recent survey¹ of the rôle played by the adrenals brings forcibly to the fore that hyperplasia of these organs, as well as certain of their neoplasms, is accompanied by a hypertension, either continual or paroxysmal in type. A hyper-adrenalism as a cause for hypertension has been treated successfully with partial bilateral suprarenalectomy.

On the other hand, a careful study of the basophilic pituitary syndrome will show that an adenoma of the adrenal cortex or a hyperplasia of the gland was also found in many of these cases. Likewise injections of pituitary extracts will bring about hypertrophy of the suprarenal cortex. Moehlig and Osius,² Smith³ and others have stressed the fact that both the pituitary and suprarenal cortex reflect the state of each other and that the pituitary is probably the dominant gland.

The syndrome of pituitary basophilism, as first reported by Cushing,⁴ indicated that hypertension was an outstanding sign. These cases with verified basophil adenomas of the anterior lobe of the hypophysis all showed a uniform symptomatology. Others also described by him, although unverified pathologically, presented the characteristic syndrome of amenorrhea or impotence, hypertrichosis, hypertension, obesity, purplish lineæ atrophicæ on the abdomen or thighs, polycythemia, plethora, osteoporosis, etc.

The pattern shown in these cases was immediately recognized by other observers. A number of variations were reported by me⁵ as appearing in patients—unverified clinical cases—all of whom presented many, if not all, of the classical signs of this condition. Williams⁶ also reported a patient 66 years of age in whom there was a psychosis of the senile type, a carcinoma, hypertension, polycythemia, purpuric spots with plethoric facies and a marked masculine hypertrichosis, but confirmation of basophilism was not verified.

In a later communication Cushing⁷ made an interesting suggestion as to the additional importance of the basophil cells, in connection with a case of fatal eclampsia in which there was found a hyperplasia of basophil cells which were invading the posterior lobe. He⁸ noted that the fully ripened elements of the pars intermedia are indistinguishable from the basophil cells of the pars anterior and that they secrete the active hormone of the posterior lobe. Massive basophilic invasion is nothing more than an exaggeration of the normal secretory process and he feels it is a reasonable explanation of the symptoms which accompany basophilic adenoma and the symptomatically related states of eclampsia and essential hypertension. This he considers is brought about by an activation of the posterior lobe by the basophilic elements. As additional evidence he cites Hofbrauer and Anselmino, who demonstrated an excess of posterior lobelike substance (antidiuretic and hemodynamic) in the blood of patients with a hypertensive form of eclampsia.

These observations and the occurrence of pluriglandular cases with only a few signs of the basophilic syndrome had led me to feel that many cases could be found in whom a basophil adenoma could not be proven, but who undoubtedly presented in part the clinical syndrome of pituitary basophilism. Following are 2 case reports which demonstrate strikingly this syndrome.

Case Abstracts. CASE 1.—C.M. (Fig. 1), male, aged 32, was admitted to the surgical ward, St. Luke's Hospital, December 26, 1933, because he had felt something snap in his chest while he was lifting a bookcase on the previous day. Several hours after the accident he coughed up some blood. He had been examined 3 years previously for life insurance and at that time was found to have diabetes. On admission to the hospital he had slight polyphagia, polydipsia and nocturia. There was some impotence. For many years he had suffered off and on from headaches located bifrontally and parietal. Examination and Roentgen ray studies revealed a fracture of the sixth, seventh, eighth and ninth ribs. He was then transferred to the medical service of Dr. L. F. Frissell where a complete survey of his condition was made.

Physical examination showed a man of medium height, plethoric and ruddy, with slight exophthalmos. He was rather obese with marked abdominal adiposity. The thyroid was not palpable and the hands were short with rather square fingers. The hair growth was profuse, with heavy eyebrows and beard and marked hypertrichosis on limbs and abdomen (Fig. 2). On the abdomen below the navel were purpuric lineæ atrophicæ radiating from the base of the pubes up over the abdomen with some striae also on the thighs and transverse in the suprailiac region. Eye grounds

(Dr. A. Wiener) showed a blurred optic disk with tortuous arteries and hemorrhages scattered through the retina—the characteristic picture of a diabetic retinitis. The visual fields were normal. The blood pressure was 180/130. The laboratory examinations were as follows: Hemoglobin, 110%; red cells, 4,700,000; white cells, 12,600; neutrophils, 90%. The urine showed a specific gravity of 1.006, faint trace of albumin and no sugar, acetone or diacetic acid. The blood sugar showed 165 mg. per 100 cc.; calcium, 10.3 mg.; phosphorus, 2.6 mg. The blood sugar curve was 125–250–308–200–167 mg. The urine sugar the second hour was 1.05 gm.; the fourth hour, 2.15 gm.; the sixth hour, 0.56 gm., and the eighth hour, negative. The basal metabolic rate was -23% . There were no changes in the spinal



FIG. 1.—Case 1 showing slight exophthalmos, hirsuties and abdominal striae.

fluid. Roentgen rays of the skull showed the sella turcica to be of average size. There was no erosion. The frontal sinuses were small and a mottling and granular appearance of the skull throughout was noteworthy. Through the basal region and the sella there was a thinning out of the bone. Anteriorly, the bones presented a finely granular appearance which suggested a loss of calcium.

A second admission on March 24, 1934, was necessary because of swelling of the ankles and increasing dyspnea. At this time examination revealed flushed plethoric facies with slight exophthalmos; the heart was enlarged and there was a systolic murmur at the apex and an accentuated aortic second sound. The blood pressure was 180/140; the liver was enlarged 3 inches below the costal margin and was tender. The eye grounds showed

hyperemic disk with spots of degeneration and exudate. The fields were normal. Laboratory examinations revealed urea nitrogen, 17 mg.; sugar, 286 mg.; CO_2 , 52%. The Wassermann test was negative. The specific gravity of the urine was 1.008; there was a trace of albumin; 3% sugar; no acetone or diacetic acid and occasional hyalin and granular casts. Radiation of the pituitary was recommended on April 4, 1934, and 4 treatments were given during which time the patient was relatively well and allowed to go home. He remained in this state until 4 days before his third admission—June 15, 1934. On admission there was cyanosis, Cheyne-Stokes breathing, plethoric facies, abdominal striae, hypertrichosis of the body, small genitalia. There were fine and coarse râles in the lungs and roughened

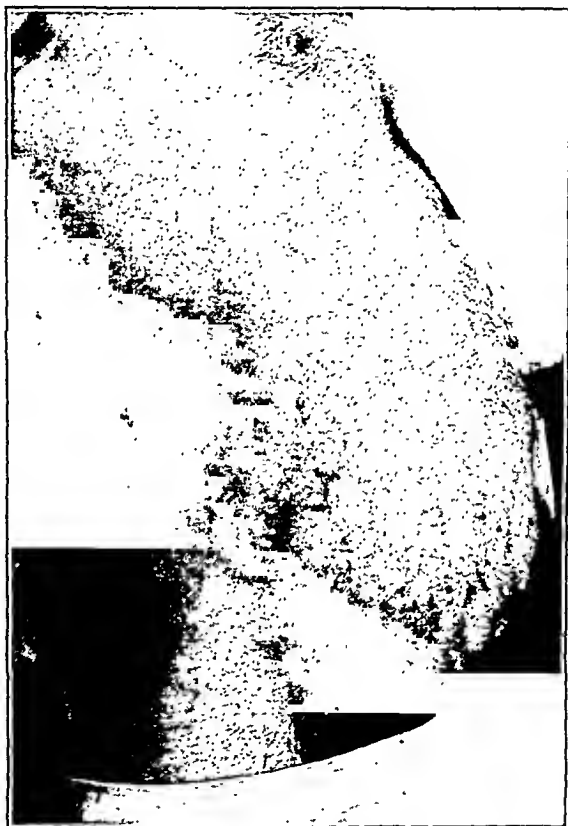


FIG. 2.—Case 1, demonstrating abdominal adiposity with purplish lineae atrophicae.

breath sounds. An electrocardiogram at this time demonstrated myocardial damage. The blood pressure was 195/125. The basal metabolic rate was -16 and -25%. The blood count was normal. The blood chemistry showed the urea nitrogen, 22.7 mg.; uric acid, 6.4 mg.; creatinin, 1 mg.; sugar, 285 mg.; CO_2 , 46.6%. On July 6, the urea nitrogen was 15.7 mg.; sugar, 125 mg.; CO_2 , 37.4%; uric acid, 6.4 mg.; creatinin, 1 mg.; cholesterol, 278 mg. The blood pressure readings were 205/150; 184/140; 180/150; 164/100, 176/110. He was treated with diet, insulin, chloral hydrate and digitalis. His condition improved and he was again allowed to go home.

He was admitted again on August 28 for the fourth time, with cough, hemoptysis, insomnia, pain in the right upper quadrant, dyspnea and edema of the legs. He had been active since his discharge from the hos-

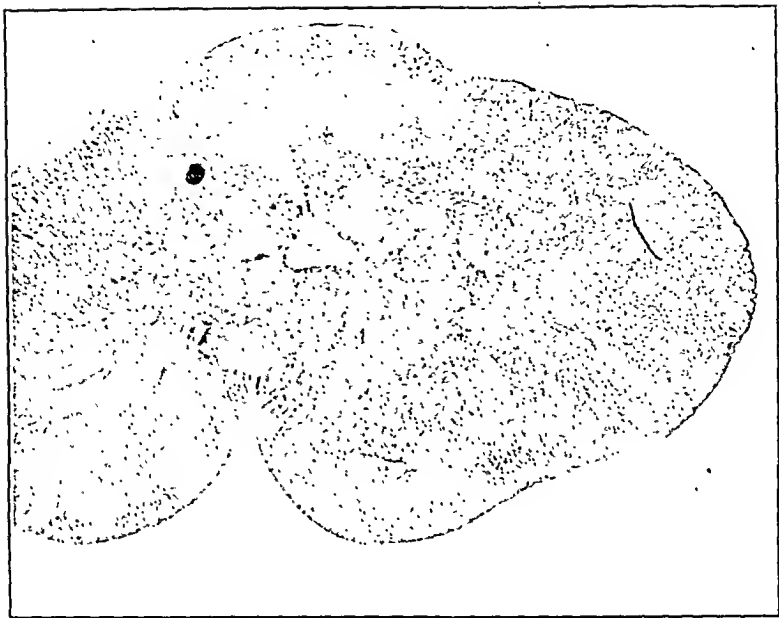


FIG. 3.—Section of adrenal gland ($\times 7$), showing moderate enlargement and beginning hyperplasia.



FIG. 4.—Section of hypophysis ($\times 7$), showing hyperplasia of basophil cells, though no actual circumscribed adenoma.

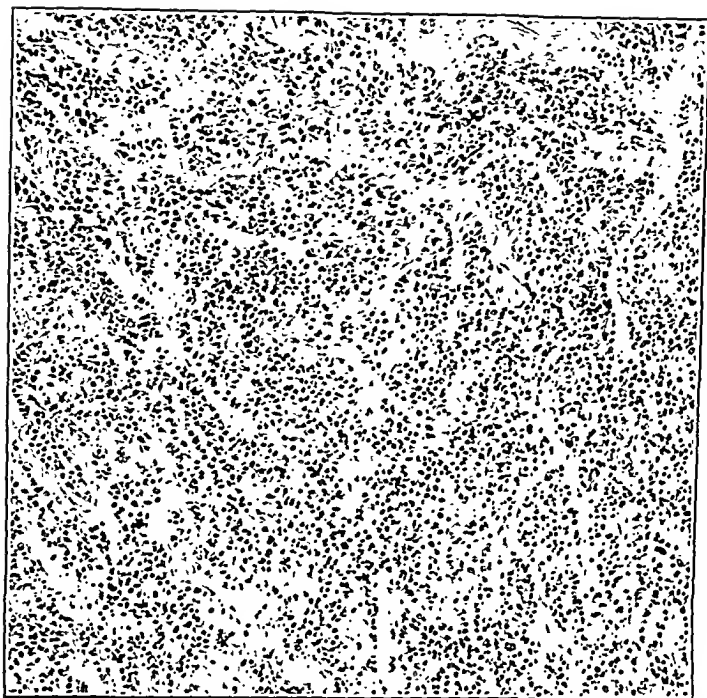


FIG. 5.—Section of anterior lobe ($\times 150$) as indicated on Fig. 4 as *B*; showing hyperplastic cords of basophil cells.



FIG. 6.—Section junction of pars anterior and pars nervosa ($\times 200$) showing invasion by basophil cells into the non-glandular portion.

pital. Examination showed respiratory distress, cyanosis, flatness in lungs posteriorly, with diminished tactile fremitus and breath sounds, crepitant râles at base, heart enlarged to the left, blood pressure 250/130, pouty abdomen, no fluid, liver 1 inch below the costal margin, and edema of the hands and feet. Roentgen ray of the chest revealed markedly enlarged heart with haziness at base of both lungs. He ran a febrile course—temperature, 102° F.—and rapid pulse, developed pneumonia in the right chest and died.

Autopsy. Lungs: Congestion and edema of the right upper and middle lobes with consolidation of the lower. The left lung presented some pneumonic infiltration in the lower part of the upper and in the lower lobe.

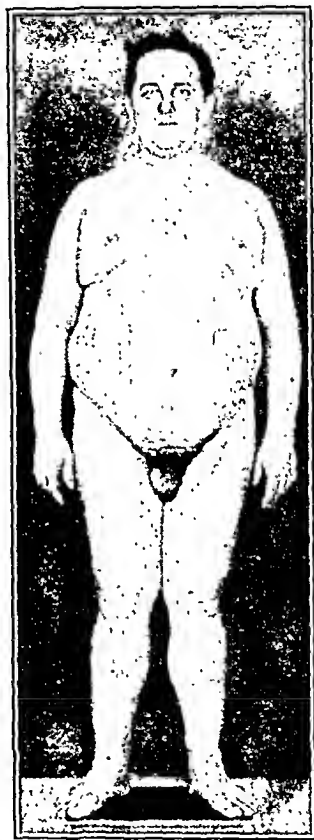


FIG. 7.—Case 2. Abdominal adiposity of hypopituitary type.

The pericardial sac contained 500 cc. of fluid, the surfaces were smooth, the left ventricle was hypertrophied, the valves were competent, there was atheroma in the arch and in the abdominal aorta. The liver extended 8 cm. below the xiphoid cartilage and had a nutmeg mottling appearance throughout. The spleen, pancreas and kidneys showed nothing on gross examination. The adrenals showed a slight diffuse increase in the size of the organ (Fig. 3). The pituitary gland weighed 0.72 gm. It was firm and slightly, though definitely, enlarged (Fig. 4). Section revealed several diffuse elongated whitish areas in the anterior lobe. The sella turcica was normal in contour and the clinoid processes were well preserved. The cellular elements in the pituitary showed a striking predominance of basophils, con-

centrated toward the border between the lobes and a direct invasion of the posterior lobe (Figs. 5 and 6).

Anatomic Diagnosis. Massive bronchopneumonia of both lungs, serous pericarditis, left ventricular hypertrophy, myocardial fibrosis, chronic passive congestion of the lungs, liver and spleen.

CASE 2 (Fig. 7).—J. R., male, aged 37, presented himself at the outpatient department at St. Luke's Hospital in January, 1934, for examination. He had for some years been a donor for blood transfusions and reported that he always felt better after giving blood. He has always been fat and well. He had had bitemporal headaches off and on for some time.



FIG. 8.—Case 2, showing purplish lineæ atrophicæ on abdomen and in axillæ.

Physical examination showed a man of medium height with generalized obesity, but especially marked about the abdomen. Slight exophthalmos was present and there were purplish lineæ atrophicæ on the abdomen (Fig. 8). The genitalia were small. The heart was slightly enlarged. The skin was pale and there was the average amount of body hair. The blood pressure was 170/110. *Laboratory examinations:* Hemoglobin, 101%; red blood cells, 5,450,000; white blood cells, 7100, and neutrophils, 76%. The blood Wassermann test and the urine were negative. The basal metabolic rate was +19%. A Roentgen ray of the skull showed the sella turcica to be of average size and there was no erosion.

This case presents exophthalmos, headaches, obesity, hypertension, purplish abdominal striae, polycythemia, small genitalia and loss of libido—a group of signs which are characteristic of the basophilic syndrome. The occurrence of the blood changes therein is no doubt a factor in making the patient able to pursue his occupation as a donor.

Discussion. By the finding of basophilic hyperplasia of the pituitary in a patient suffering from hypertension, diabetes and many of the classical signs of pituitary basophilism, it is possible to forge another link in the chain of evidence implicating the hypophysis in certain clinical states associated with hypertension. This patient showed also abdominal adiposity, plethora, polycythemia, purplish lineae atrophicæ, hypertrichosis, changes in the bony structure suggesting decalcification, exophthalmos, glycosuria and small genitalia and impotence.

This grouping of signs has been associated with a basophilic adenoma of the pituitary and will link up that syndrome with those cases reported by Cushing,^{9,10,11} A significant report by Graef, Rottion and Bunim¹² on a case of hypertension, glycosuria, purplish abdominal striae associated with an adrenal tumor throws some doubt upon the relationship of the pituitary to this syndrome. However, associated changes in both the adrenals and pituitary have been constantly commented upon both in clinical pathologic studies and from the results of animal experimentation. Owing to the dominant position held by the hypophysis as a regulator of activity in the thyroid, adrenals and gonads, it is not presumptuous in the light of our present knowledge to continue to regard the syndrome of pituitary basophilism as a primary pituitary disturbance.

What is the relationship then of this syndrome to hypertension? Cushing has in a larger series of observations tried to demonstrate that hyperactivation of the neurohypophysis by a basophil cell hyperplasia and posterior lobe invasion is the rule in certain types of hypertension. Eclampsia, essential hypertension and the hypertension of the arteriosclerotic are evidently often accompanied by a basophilia, which apparently activates the posterior lobe and increases its humoral output. Just what the hormone secreted from the basophil cells may represent in hypophyseal activity is a point yet to be determined; nor is it yet certain that the sex hormone arises from these cells. A pressor substance from the posterior lobe has long been recognized and the neural connection with the hypothalamic centers is an accepted anatomic and functional fact. On the other hand, a conclusion as to etiology of hypertension in these basophilias is impossible without a consideration of its association with the adrenal glands. The known relationship between these glands and their important vegetative connection must be further understood before evaluation of hypertension can be made.

We are ready to consider that the hypertension of pituitary

basophilism may be associated with either a basophilic adenoma or a basophilic hyperplasia and invasion of these cells into the pars nervosa. A case showing this situation is reported with autopsy, and a second one, still living, is shown with a typical clinical picture. It would seem worth while in the light of these 2 cases to scan carefully our medical clinics for further confirmation of this interesting relationship.

Summary. 1. The clinical syndrome of pituitary basophilism is protean, being reported with basophil adenoma, adrenal adenoma and other unverified cases.

2. One case reported with a hypertensive plethoric syndrome characteristic of pituitary basophilism was found to have a basophil hyperplasia of the hypophysis.

3. A second case with a less marked simulation of the classical syndrome is presented.

4. Additional evidence is offered that hyperplasia of the basophil cells of the anterior pituitary may induce a hypertension and a typical syndrome of pituitary basophilism as well.

5. It behooves us therefore to investigate further the pituitary—adrenal—diencephalic complex as a basic cause for hypertensive states.

I should like to express my indebtedness to Dr. Lewis F. Frissell, Director of Medical B Service of St. Luke's Hospital, New York, for the privilege of reporting these cases from his Wards and Clinic, and to Dr. Liela C. Knox for coöperation in the pathologic study.

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A SYNDROME, SIMULATING DIENCEPHALIC STIMULATION OCCURRING IN PATIENTS WITH ESSENTIAL HYPERTENSION.

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THE similarity between the reaction in human beings to β -methyl-acetyl-cholin and the reaction to stimulation of diencephalic centers has recently been pointed out by Page.¹ Since observing this reaction, its great similarity to a spontaneous syndrome occurring usually in young patients (ages 18 to 29) suffering from essential hypertension has become evident. In the past 2 years 11 such patients have been studied. Following is a description of what was observed to a more or less marked degree in all of the patients:

Attacks arise spontaneously at times, but are usually brought on by excitement. A blush first appears over the forehead and cheeks, spreading down to the neck and trunk. Particularly over the trunk it is blotchy, but often becomes confluent. Over the reddened area tiny beads of perspiration appear. The legs and arms are rarely involved, and the hands, especially the fingers, may be cyanotic and cold. The heart rate increases and the patient may complain of palpitation. The blood pressure rises moderately (20 to 30 mm. Hg). The eyes water, or actual crying occurs. Salivation may take place, and the patients often state that they feel choked. Respiration is less frequent, deeper, often sighing, and may become labored. Movement of the intestine is felt by the patient and often can be heard by an observer.

These signs and symptoms seldom last for more than a few minutes, but may occur a number of times in a day with greatly varying intensity.

The syndrome has been observed in this fully developed form largely in young women. Without exception the disease has been severe, as evidenced by high blood pressure (averaging 220 mm. systolic and 146 mm. Hg diastolic), and in 1 case by a rapidly fatal outcome. Other characteristics were sexual frigidity, profuse menstruation and high-strung temperament. Often tremor of the hands was present, and attacks of general trembling were not uncommon. Slight enlargement of the thyroid gland was often observed; the basal metabolism was either normal or slightly elevated (+5 to +20). Sensitiveness to cold and a complaint either of "dead fingers" or of numbness of the hands on exposure to cold were frequent. Ringing in the ears, nausea, and a feeling of tightness of the scalp over the vertex were common complaints.

While this syndrome was most commonly observed in girls and young women, various components of it have often been seen in older patients. Especially common are perspiration, flushing and palpitation. Older patients whose blood pressure has long been fixed at a high level rarely exhibit it.

The mechanism of the syndrome is unknown, but it has so many features characteristic of stimulation of the centers within the diencephalon that it seems profitable to examine the evidence suggesting its origin at this site in detail.

Neurologists believe that the hypothalamus is the essential instrument of emotional expression. Upon it rests the responsibility for translating into behavior the initiative to action which is taken by the cerebral cortex.² It is indeed this part of the brain which organizes, by means of the sympathetic and parasympathetic systems, the most vital activities of the body itself, its visceral functions, its growth and metabolism, and even such appetites as those of sex. More especially, it is in the neopallium (*e. g.*, the non-olfactory cortex) that control of such activities is most highly concentrated. Nervous impulses circulate through the brain to effect coordination between the instruments of the conative dispositions and those of the affective (thalamus) and the cognitive (neopallium) dispositions of the mind. This mechanism involves the hypothalamus, which presumably sets the emotional tone that colors all mental and muscular activity, in particular in artistic expression and self-consciousness.²

Experimental proof of the function of the diencephalon in the emotional activation of the sympathetic nervous system has been supplied by the observations of Cannon and Britton,³ but more especially by Bard.^{4,5} They were able to bring about a state which they called "sham rage" in cats by removal of the cerebral hemispheres. Such signs of widespread sympathetic activity were apparent as erection of hair, rapid heart rate, profuse sweating at the toe pads, high arterial pressure and discharge of epinephrin. The disposition to exhibit behavior which is primitively emotional, comparable to that which enables the normal animal to meet critical situations in life, gives strong support to the view that the nervous mechanisms for the expression of rage are subcortical. The influence of the cortex in this reaction may actually decrease rather than increase that exerted by the subcortical mechanisms (Bard). Bard adopts the view, first advanced by Hughlings Jackson and elaborated by Head, that the cortex normally holds in check those activities of the lower and more archaic centers, the unrestrained action of which would seriously interfere with its more discriminative reactions. He regards action of the caudal half of the hypothalamus and the most ventral and most caudal fractions of the corresponding segments of the thalamus as the portions responsible for the exhibition of sham rage. The diencephalic

mechanism is activated during times of stress and emergencies, and is responsible for the widespread nervous discharge which then occurs.

Both sympathetic and parasympathetic centers are believed to exist within the hypothalamus. The anterior group may be "parasympathetic" because of the relationship of the tuberal nuclei to the craniosacral division of the autonomic nervous system with its peripheral control through vagus and pelvic nerves.⁷ The posterior groups, in the walls of the posterior portion of the third ventricle above the corpora mammillaria, are said to contain the sympathetic centers.

At lower levels, bulbospinal centers exist which normally suffice for tonic and reflex sympathetic discharges. They can act independently, but may be influenced by centers at a higher level.

Cushing⁶ has supplied strong evidence for locating in man the presence of parasympathetic centers in the hypothalamus by injecting various substances into the ventricles. Vasodilatation, sweating, lacrimation, salivation, increased peristalsis and vomiting occurred. A small discrete encapsulated tumor, so placed as to impinge upon the anterior and superior portion of the thalamus on each side, was found in a patient to elicit at first restlessness, then sudden intense dilatation of the vessels of the face, arms and breasts, sudden rise in blood pressure, lacrimation, sweating, salivation, increase in heart rate, retardation of respiratory rate and hiccoughs, ending with transient shivering.⁷ Clearly these attacks, which Penfield called "diencephalic autonomic epilepsy" are explosive, undiscriminating discharges which suggest the proximity of a lesion (tumor) both to parasympathetic and sympathetic centers. The promotor area of the cortex may also participate in the genesis of symptoms believed to be characteristic of central autonomic discharge. Irritation caused by the growth of a tumor often results in increased sweating and vasodilatation on the contralateral side of the body.⁸

In the syndrome observed in patients suffering from essential hypertension, a marked resemblance to that due to different causes and described by Cushing, by Penfield and by Page, is apparent (Table 1).

Clinical experience suggests, accordingly, that in essential hypertension there is evidence of diencephalic irritation. Emotional instability akin to sham rage in cats is a regular occurrence. Phenomena are observed in these patients which suggest strongly regression to more archaic emotional patterns. Their similarity to syndromes resulting from diencephalic stimulation lead to the belief that they, too, have their genesis in the diencephalon.

Case Abstracts. Case 1 (No. 9193).—P. S., female, aged 25. The blood pressure was known to have been normal until 1½ years ago. About 14 months ago the patient noticed that she tired very easily, and that she had

frequent severe headaches. She became restless, sleepless, irritable and complained of "spells" during which she had an uncontrollable desire to yawn and cry. Simultaneously her face felt flushed and hot. Her blood pressure was found to be 182/116 mm. Hg; and urea clearance 91.5% of normal. Fundus examination showed very early arteriolar sclerosis with moderate sausage-shaped arteriolar constriction.

TABLE 1.—SYMPTOMS OF DIENCEPHALIC IRRITATION.

	Essential hypertension.	Acetyl- β -methyl-cholin.	Diencephalic epilepsy.	Intraventricular puitritin.
Probably parasympathetic	Sweating Vasodilatation Lacrimation Salivation Increased peristalsis Slowed respiration Deepened respiration	Sweating Vasodilatation Lacrimation Salivation Increased peristalsis Slowed respiration Deepened respiration Fall in blood pressure	Sweating Vasodilatation Lacrimation Salivation Slowed respiration Deepened respiration	Sweating. Vasodilatation Lacrimation. Salivation. Increased peristalsis. Slowed respiration. Deepened respiration. Slight slowing of heart rate.
Probably sympathetic	Slight rise in blood pressure Increased heart rate Excitement Increased heart rate	Rise in blood pressure Increased heart rate	Slight rise in blood pressure.
Possibly control release	Fits of uncontrollable anger Excessive irritability	Restlessness	

CASE 2 (No. 8990).—I. S., female, aged 23, has been very much worried over a love affair for the past 16 months. During the last year she noted that she tired easily. Because of her irritability and uncontrollable outburst of temper her blood pressure was measured and found to be elevated. She complains of excessive perspiration most of the time, and often has attacks of violent blushing. Lacrimation and salivation usually accompany the blushing. She states that while she realizes that her behavior only makes her condition worse, she is unable to control herself. The blood pressure was found to be 196/116 mm. Hg; urea clearance 69% of normal. The eye grounds appear normal except for slight arteriolar constriction. Basal metabolism, +7.

CASE 3 (No. 9101).—E. J., female, aged 24, has always been a very nervous person. She noticed for the past few years that she perspires and blushes without any apparent cause, and in the past year the blushing attacks have become very troublesome. Simultaneously she has palpitations, a feeling of tightness and uneasiness in the abdomen and is apt to cry. Tinnitus aurium is almost constantly present. About twice a year she has had attacks strongly suggesting epilepsy. Blood pressure was found to be 208/140 mm. Hg; urea clearance 91.5% of normal. The disk of the fundus is hyperemic, the arterioles tortuous and very slightly constricted, the veins are moderately tortuous and dilated.

CASE 4 (No. 8554).—M. G., female, aged 24, 5 years ago noticed attacks of blurred vision, dizziness and profuse perspiration. Always excitable, in the past few years she has become very irritable and restless. She has attacks of "choking" during which she states she has to breathe very deeply, associated often with flushing and crying. Blood pressure, 248/146 mm. Hg; urea clearance, 87.2; basal metabolism, +33. Moderate constriction and early arteriosclerosis of the arterioles in the fundus was observed.

CASE 5 (No. 9278).—A. S., female, aged 24, first noticed 4 years ago that after emotional excitement her face and upper chest became blotchy

and that she had spots before her eyes and was dizzy. Her systolic blood pressure was found to be 130 mm. She became extremely nervous and irritable 7 months ago and exhibited almost all of the signs and symptoms of "diencephalic irritation." Blood pressure was found to be 210/136 mm. Hg.; urea clearance, 80% of normal; basal metabolism, +15. Slight, if any, constriction of the arterioles of the fundus was observed.

CASE 6 (No. 9317).—R. H., female, aged 17, first suffered 3 years ago from attacks of dizziness and headaches which prostrated her. One year ago she decided to become a nun. Physical examination showed her blood pressure to be 160. For 2 or 3 years she has exhibited attacks quite characteristic of "diencephalic irritation." Unquestionably she suffers from emotional instability and conflict. Blood pressure was found to be 174/118 mm. Hg; urea clearance, 108% of normal; basal metabolism, +4. Moderate tortuosity of the retinal arterioles and but slight constriction was observed.

CASE 7 (No. 9306).—B. H., female, aged 32, has been a high strung, emotional person for the past 10 years or more. Irregularity in her sexual activity has caused much difficulty in her life. Vasomotor instability, as shown by mottled blushing of her face and upper chest with palpitations, has been present for many years. The blood pressure was found to be elevated 8 years ago. At present it is 190/120 mm. Hg; urea clearance, 97% of normal; basal metabolism, +21. The eye grounds are normal.

CASE 8 (No. 9339).—A. R., female, aged 25, for the past few years has noticed attacks quite typical of those described as "diencephalic irritation." Two years ago her blood pressure was found to be 140. It has gradually risen to 200 and now varies from 170 to 230 mm. Hg systolic, and 108 to 138 mm. Hg diastolic; urea clearance, 73% of normal; basal metabolism, +11. The eye-ground disks are hyperemic, the arterioles constricted and the veins dilated. There is very slight perivasculitis.

CASE 9 (O.P.D.).—E. C., female, aged 36, has had many emotional conflicts. She has shown evidence of "diencephalic irritation" for the past 3 to 4 years. Two years ago her blood pressure was normal but is now 162/98 mm. Hg. Urine is normal and no pathologic changes are observed in her eye grounds.

Summary. A syndrome has been described which is observed in its fully developed form largely in young women suffering from essential hypertension, but components of which may occur in many cases of essential hypertension. The signs and symptoms so closely resemble those resulting from irritation of sympathetic and parasympathetic centers in the diencephalon, and possibly the promotor area of the cortex, as to suggest that they originate there. Phenomena also occur in these patients which suggest strongly regression to more archaic emotional patterns, possibly having their genesis in the thalamus and hypothalamus.

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THE EFFECT OF ADRENALIN INJECTION ON THE BLOOD OF PATIENTS WITH AND WITHOUT SPLEENS.

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RECENT studies on the effect of adrenalin injection on the blood picture have been influenced so much by Barcroft's^{1,2,3} work on the physiologic contraction of the spleen that sight has been lost of early literature on this subject. This has been reviewed ably by Kagi,⁴ Edmunds and Stone,⁵ Lamson^{6,7} and recently by Benhamou.⁸

Although certain investigators find no constant changes in the blood response after the injection of adrenalin, in general the literature records leukoeytosis and polycythemia. Some authors^{9,10} find a characteristic leukocyte formula with lymphocytosis rapidly followed by neutrophilic leukocytosis. The cause of the white blood cell increase has been variously attributed to stimulation of the vegetative nervous system;¹¹ to a chemotactic reaction;^{12,13} to direct stimulation of myeloid and lymphoid tissue;⁵ to functional state of lymphoid tissue;¹⁴ to mechanical alteration in the blood stream;⁴ to unequal redistribution of cellular elements;¹⁵ and to contraction of the spleen with expulsion of stored cells.^{9,16,17}

An increase of red blood cell and hemoglobin concentration following injection of adrenalin also has been observed in animals and man.^{6,16,17,18} Its cause is debated. Earlier workers have ascribed the effect to hemoconcentration. Lamson,⁶ for example, believes it is due to constriction of the hepatic veins with loss of plasma. More recent publications^{16,19} imply an outpouring of cells from the spleen, despite the fact that increases of blood volume were not obtained.

It is beyond the scope of this paper to evaluate the exact nature of the adrenalin effect on the blood picture. It does, however, seem timely to determine whether or not this drug acts by squeezing from the spleen a reserve supply of blood. Studies with this objective have been made previously by Frey²⁰ and Edmunds and Stone⁵ on animals. In rabbits Frey found the characteristic leukocytosis wanting after splenectomy. In guinea pigs extirpation of the spleen made no difference in the response. Edmunds and Stone found that an increase of white cells, red cells and hemoglobin occurred after adrenalin injection in dogs whether the spleens were intact or removed.

Since observations on animals may be misleading when compared with responses observed in man, it is pertinent to review previous clinical studies where a comparison has been made between patients with and without spleens present. Kreuter²¹ and Frey²⁰ each reported a case in which leukocytosis occurred following adrenalin injection in a splenectomized patient. Schenk²² did studies on patients with splenomegaly and on 3 patients after splenectomy. Following the subcutaneous injection of 1 to 2 mg. adrenalin there occurred a rise of red blood cells, hemoglobin and white blood cells in all instances.

Yang¹⁷ did a similar study on 3 normals, 4 patients with splenomegaly and on 2 splenectomized patients. There occurred an average increase of about 400,000 red blood cells and 4% hemoglobin in patients with splenomegaly after subcutaneous injection of 0.5 to 1 cc. of 1 to 1000 adrenalin hydrochlorid. No significant alteration in red blood cell or hemoglobin concentration of the normal and splenectomized patients took place. With this moderate gain in red blood cells and hemoglobin, it is not remarkable that subsequent blood volume studies¹⁹ showed no appreciable change. This failure was attributed to a CO method which was believed to record falsely elevated initial values because of absorption of the gas by the spleen.

Recently Benhamou⁸ reported results of studies similar to those of Yang. A moderate transitory increase of red blood cells and platelets occurred except in the splenectomized patients. This difference was attributed to the absence of the spleen in the latter cases. However, persistent leukocytosis was observed in all instances, and he therefore concluded that the white blood cell increase was not a function of splenic contraction.

Because of the diverse results and the difficulty in the interpretation of the blood changes produced by adrenalin injection, we felt there was need of determining whether or not the spleen actually was significantly involved in the reaction.

Methods. Blood studies were, therefore, made before and after the subcutaneous injection of adrenalin on 2 normal persons, on 9 patients with

chronic hemolytic jaundice—5 with spleens and 4 without spleens—and on 6 patients with splenomegaly associated with various other diseases.

In each patient a single subcutaneous injection of adrenalin hydrochlorid, 1 to 1000 dilution (Parke-Davis), in doses of 0.8 to 1 cc. was made. The patients experienced characteristic reactions with tachycardia, elevated blood pressure, palpitation, sweating, nervousness and tremor.

Three venous blood samples were obtained in each case, using 0.05 cc. of 20% potassium oxalate as an anticoagulant for 5 cc. of blood. The first sample was taken just before the adrenalin injection; the second, 15 minutes after the injection; the third, several hours later. Capillary blood samples were taken at the same time as the venous blood and an additional capillary sample was taken at 5 minutes after the adrenalin injection. The 5-minute and 15-minute observations were made because the marked effects described by other workers have occurred during the first 15 minutes. The times for the final sample were varied in the hope of finding the optimal time for observing a delayed response.

Red blood cells were enumerated by averaging the counts in two chambers. Hemoglobin was determined in duplicate, using a Sahli hemometer so calibrated that 100% corresponded to an oxygen capacity of 21 volumes of oxygen per cent. This was assumed to be the oxygen capacity of 15.6 gm. of hemoglobin. Hematocrit studies were done and indices determined according to the Wintrobe method.²³ Total white blood cell and platelet counts were made from capillary blood from the ear lobe as well as differential white blood cell counts of 200 cells and determinations of the percentage of reticulocytes in 1000 red blood cells.

Results. The blood studies on 2 normal persons and on 4 splenectomized patients with hemolytic jaundice are recorded in Table 1. The red blood cell and hemoglobin concentrations are seen to have fluctuated no more than may be expected to arise from technical error. Detailed hematocrit indices also were determined, but the changes observed were very small and were regarded as insignificant. Increases of white blood cells, however, appeared to be constant and prolonged. This increase involved neutrophils, lymphocytes and monocytes. For the cases of hemolytic jaundice with spleens, the average white cell counts and the average absolute counts of the different white cells are plotted in Chart I. Young neutrophils showed an immediate decrease and later a return up to and exceeding the initial levels. For the most part these remained within the normal range of 2% to 5%. Reticulocytes in both absolute and percentage numbers were essentially unchanged following the injection of adrenalin. In 3 cases of this group there was a moderate increase in the number of blood platelets after adrenalin injection.

In Table 2 a similar tabulation is made for observations on 5 patients with hemolytic jaundice and splenomegaly. In 2 of these patients (Cases 1 and 5) there occurred a definite but merely transitory increase in red blood cell and hemoglobin concentration. An increase of total white blood cells, involving neutrophils, lymphocytes and monocytes, took place in every instance after adrenalin injection. Here, too, as in Table 1, there was a tendency for young neutrophils to decrease and later to increase in number, but never exceeding in per cent the normal range of such cells. No sig-

nificant change in number of reticulocytes occurred. The average total white cell counts of this group are plotted in Chart I as well as the average absolute counts for the different kinds of white blood cells.

TABLE 1.—OBSERVATIONS ON THE BLOOD PICTURE BEFORE AND AFTER SUBCUTANEOUS INJECTION OF ADRENALIN HYDROCHLORID, 0.8 TO 1 CC., IN 2 NORMAL SUBJECTS AND 4 SPLENECTOMIZED PATIENTS WITH CHRONIC HEMOLYTIC JAUNDICE.

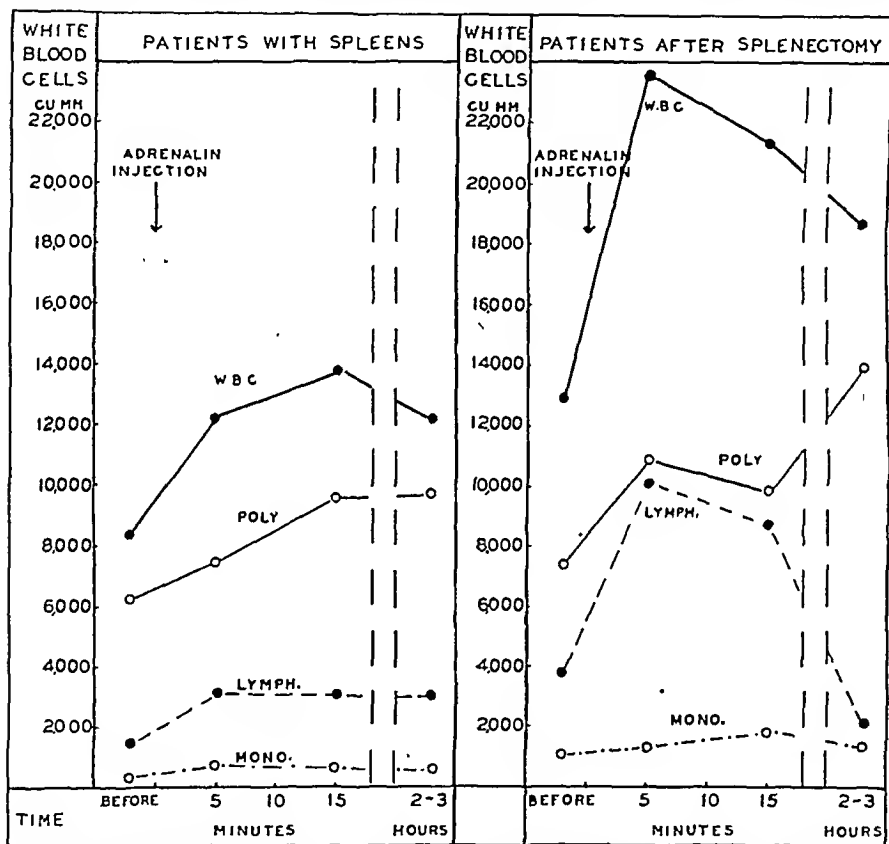
Case.	Time.	Red cells, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Hematocrit, per cent.	Platelets, thousands per c.mm.	White cells, per c.mm.	Neutrophils, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Young neutrophils, per c.mm.	Young neutrophils, per cent.	Reticulocytes, per cent.
<i>Normals.</i>												
1 . .	Before	4.88	14.5	42.0	..	9,700	5,820	3,004	436	183	1.9	
	5 min.	7,850	5,102	1,884	588	76	1.0	
	15 min.	4.87	14.4	42.3	..	9,450	6,234	2,268	614	125	1.3	
	4½ hrs.	4.88	14.7	43.8	..	10,700	7,222	2,407	856	289	2.7	
2 . .	Before	4.96	14.8	42.7	..	7,400	3,737	2,300	888	150	2.0	0.8
	5 min.	10,600	4,823	4,300	1000	320	3.0	0.6
	15 min.	4.97	14.8	43.0	..	12,300	6,396	3,870	1600	126	1.0	0.8
	1 hr.	5.09	14.6	42.7	..	10,600	5,883	3,000	800	270	2.5	1.0
	3½ hrs.	4.90	14.8	43.2	..	12,600	8,820	1,950	1260	380	3.0	0.6
<i>4 Splenectomized Patients With Chronic Hemolytic Jaundice.</i>												
1 . .	Before	5.55	18.8	52.4	402	8,800	4,400	2,500	1100	89	1.0	0.6
	5 min.	364	16,950	5,560	9,237	1186	83	0.5	0.4
	15 min.	5.55	18.7	50.9	467	17,900	6,470	7,876	2236	65	0.4	0.2
	4 hrs.	5.64	18.8	48.8	389	14,425	7,600	2,957	1658	315	2.2	0.3
2 . .	Before	5.92	17.5	49.1	..	16,000	8,560	5,280	1520	86	0.5	1.0
	5 min.	32,000	14,700	14,080	1600	300	0.9	1.8
	15 min.	5.95	17.3	48.5	..	30,600	13,800	11,484	3521	139	0.5	1.4
	4 hrs.	6.04	17.3	46.3	..	22,200	17,840	1,554	1110	457	2.0	1.7
3 . .	Before	4.69	13.6	38.2	366	9,350	5,300	3,179	467	92	0.5	1.1
	5 min.	468	22,000	12,440	7,810	1100	375	1.7	0.6
	15 min.	4.46	13.4	37.8	..	15,500	7,480	7,595	232	209	1.3	1.0
	3½ hrs.	4.02	12.0	36.6	428	17,850	14,300	1,785	1071	641	3.5	0.9
4 . .	Before	4.43	14.0	42.6	828	17,470	11,181	4,455	1136	437	2.5	1.3
	15 min.	1002	21,250	11,582	7,969	1275	212	1.0	1.2
	1 hr.	4.50	14.0	41.4	1030	26,780	17,942	6,829	1740	133	0.5	2.2
	2 hrs.	4.37	14.0	41.6	950	20,300	16,139	2,030	1522	406	2.0	1.9

NOTE.—Counts of basophils and eosinophils were not tabulated because their numbers were not regarded as significantly altered.

In Table 3 a similar series of observations is recorded for patients with splenomegaly associated with various diseases. Cases 1 to 4, inclusive, had chronic myeloid leukemia; Case 5 had osteosclerotic anemia and Case 6, polycythemia vera. Although the data are not so complete as in the other groups, one can observe that no appreciable change occurred in red blood count or hemoglobin except in Case 1, where a moderate rise took place; that an increase of white blood cells likewise was the rule. Under the heading "young neutro-

phils" are included myelocytes and myeloblasts. In several cases these appear to be increased in absolute and percentage numbers after the injection of adrenalin. However, the white cell distribution in leukemia is notoriously unstable and the changes observed may not be interpreted strictly as part of a causative sequence.

CHART I.—Illustrating changes in the absolute number of white blood cells before and after the subcutaneous injection of adrenalin in patients with chronic hemolytic jaundice.



Although absolute white blood cell changes appeared to be more labile after splenectomy than when spleens were intact, the percentage increase was not very different in the two groups of cases.

Discussion. It is obvious from the data presented that little difference was noted in the effect of adrenalin upon the peripheral blood values in hemolytic jaundice in patients with or without spleens. The fact that similar results were obtained in a miscellaneous group with splenomegaly indicates that the lack of difference is not due to a peculiarity of the disease, hemolytic jaundice. Moreover, this disease should be ideal for demonstrating a change in the blood picture following adrenalin injection, since it is charac-

terized by marked congestion and cellularity of the splenic pulp with little fibrosis or thickening of the capsule.

TABLE 2.—OBSERVATIONS ON THE BLOOD PICTURE BEFORE AND AFTER SUBCUTANEOUS INJECTION OF ADRENALIN HYDROCHLORID, 0.8 TO 1 CC., IN 5 PATIENTS WITH CHRONIC HEMOLYTIC JAUNDICE.

Case.	Time.	Red cells, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Hematocrit, per cent.	Platelets, thousands per c.mm.	White cells, per c.mm.	Neutrophils, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Young neutrophils, per c.mm.	Young neutrophils, per cent.	Reticulocytes, per cent.
1 . .	Before	3.13	7.8	22.1	201	1,700	3,220	794	324	187	4.0	14.3
	5 min.	3.88	10.5	32.8	249	18,600	10,825	5300	1950	335	1.8	20.3
	15 min.	3.88	10.5	32.8	243	19,000	10,835	6160	855	165	0.8	15.0
	3½ hrs.	3.03	7.9	21.6	200	9,450	7,350	945	519	403	4.2	19.2
2 . .	Before	4.70	15.6	48.7	..	7,650	5,840	1262	228	88	1.1	1.1
	5 min.	4.84	15.5	47.2	..	7,950	6,045	1431	198	155	1.9	0.7
	15 min.	4.84	15.5	47.2	..	8,350	6,370	1419	374	130	1.6	0.6
	2 hrs.	4.98	15.1	44.1	..	10,700	9,350	1070	214	50	4.7	0.7
3 . .	Before	4.04	14.5	41.7	..	10,420	8,320	1146	677	169	1.6	2.8
	5 min.	3.96	14.7	43.8	..	12,800	8,750	3136	256	88	0.7	..
	15 min.	3.96	14.7	43.8	..	15,900	11,600	2862	397	315	2.0	2.7
	3½ hrs.	3.97	15.0	41.0	..	13,770	9,900	2134	1032	523	3.7	3.0
4 . .	Before	5.21	16.7	46.5	..	11,200	7,190	2970	336	146	1.3	0.7
	5 min.	5.11	16.6	45.8	..	8,350	4,620	2840	542	94	1.3	1.2
	15 min.	5.11	16.6	45.8	..	13,250	9,300	2580	1060	188	1.4	0.8
	3 hrs.	4.91	15.7	46.0	..	14,800	11,600	1480	962	610	4.1	1.0
5 . .	Before	3.53	12.4	32.8	214	8,300	6,515	1369	124	290	3.5	11.6
	5 min.	4.32	13.3	37.3	210	13,600	10,247	1778	317	254	2.0	10.8
	15 min.	4.32	13.3	37.3	373	12,700	10,247	1778	317	254	2.0	11.4
	1 hr.	4.80	13.7	36.6	280	15,900	12,322	2600	477	397	2.5	12.0
	2 hrs.	3.67	12.3	35.0	..	12,100	10,466	1028	60	665	5.5	6.8

In spite of the fact that the doses used and the time of observations compare closely with the methods of Yang, Benhamou and others, who found red blood cell and hemoglobin increases, we failed to get constant or persistent changes in these constituents. Granted that the time of observations may have caused the response described by some authors to be missed, nevertheless such a transitory change could have little physiologic significance. In the normal dog, splenic contracture is said to increase the circulating blood volume by one-fifth.¹ If a comparable effect is produced in normal man, how much greater then should be the effect in cases with splenomegaly.

Admittedly our studies should have included blood volume determinations. The changes we observed were so trifling in the case of red blood cell and hemoglobin concentrations that we did not think at the time that blood volume determinations were essential. If we had injected larger doses of adrenalin, as Edmunds and Stone did with dogs, we might have found more pronounced effects.

In all types of patients studied there occurred a sharp leukocytosis, involving both myeloid and lymphoid cells, which subsided after

several hours. Certainly, since splenectomized patients exhibit the phenomenon as readily as those with spleens intact, this change is not a splenic function alone.

TABLE 3.—OBSERVATIONS ON THE BLOOD PICTURE BEFORE AND AFTER SUBCUTANEOUS INJECTION OF ADRENALIN HYDROCHLORID, 0.8 TO 1 CC., IN 6 PATIENTS WITH SPLENOMEGALY.

Case.	Time.	Red cells, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Hematocrit, per cent.	White cells, per c.mm.	Neutrophils, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Young neutrophils, per c.mm.	Young neutrophils, per cent.	Reti- culocytes, per cent.
<i>Chronic Myelogenous Leukemia.</i>											
1 . .	Before	4.32	15.0	44.0	4,600	2,944	841	335	300	6.5	0.6
	5 min.	5,900	3,097	1197	826	177	3.0	1.2
	15 min.	4.90	15.6	48.6	8,500	4,430	2556	724	85	1.0	1.0
	1 hr.	4.41	14.8	44.9	4,500	2,610	877	472	315	7.0	1.8
	3½ hrs.	4.07	14.0	44.0	4,850	3,273	630	606	339	7.0	1.4
2 . .	Before	3.81	12.5	34.9	184,000	69,900	2760	..	107,640	58.5	..
	5 min.	261,000	104,400	7830	1300	138,310	53.0	..
	15 min.	3.90	11.7	35.2	261,000	95,265	3915	7800	147,465	56.5	..
	4 hrs.	3.65	11.4	34.2	150,000	60,000	1500	..	85,500	57.0	..
3 . .	Before	4.62	15.6	..	37,000	31,968	370	1110	2,220	6.0	2.8
	15 min.	5.20	16.2	..	92,000	68,490	4440	1380	8,740	9.5	3.2
4 . .	Before	4.13	11.8	..	13,300	7,730	1200	1900	665	5.0	8.0
	15 min.	4.44	12.0	..	31,000	15,650	2170	4184	2,790	9.0	8.4
<i>Osteosclerotic Anemia.</i>											
5 . .	Before	2.43	6.7	..	4,150	1,743	1162	664	414	10.0	4.0
	15 min.	2.63	7.6	..	19,200	4,416	9792	2688	2,112	11.0	8.2
	2 hrs.	2.30	6.7	..	5,050	2,525	1161	252	807	16.0	5.7
	5 hrs.	2.20	6.9	..	4,750	3.8
<i>Polycythemia Rubra Vera.</i>											
6 . .	Before	7.28	19.3	..	15,200	12,060	1444	836	1.9
	15 min.	7.62	19.0	..	20,400	17,240	1938	816	2.2

No significant increase of either young white cells or of young red cells was observed. If the germinal centers, such as occur in the bone marrow, spleen and lymph nodes, were involved in the blood changes, one would expect an ejection predominantly of these young forms. This did not occur, except in certain cases of the miscellaneous group where immature cells already existed. In these instances the ratio of mature to immature forms was probably not significantly altered by the injection of adrenalin.

It is not implied that adrenalin or other drugs do not cause splenic contraction, for they most assuredly do; nor is it denied that the spleen may function as a reservoir for the circulating blood, as suggested by Barcroft. It is believed, however, because of a critical review of previous studies, particularly those of Schenk²² and

Benhamou,⁸ as well as our own, that the adrenalin test, as applied to cases with pathologically enlarged spleens, is not a measure of splenic function alone.

The red blood cell changes observed by other investigators and in 3 of our cases may be due to an outpouring from the spleen as a blood reservoir, but one should recall that there are other depots for the circulating blood—such as the liver, skin and splanchnic vessels, which are also susceptible to adrenalin stimulation. More likely an increase of red blood cells and hemoglobin without corresponding increase of blood volume would be the result of hemoconcentration. The white blood cell increase we also prefer to explain as due to a mechanical alteration in the blood stream, a theory propounded by Kagi.⁴ These cells, either pooled in inactive vascular beds or lying along the periphery of the vessel walls may be thrust into the axial blood stream by active contraction of the blood-vessels or by increased velocity of the axial flow.

Summary and Conclusions. 1. Blood studies before and after the subcutaneous injection of adrenalin were made on 2 normal subjects, on 9 patients with hemolytic jaundice—5 with splenomegaly and 4 with their spleens removed—and on 5 patients with splenomegaly from miscellaneous diseases.

2. In no case was there a significantly sustained change of concentration of the red blood cells, of hematocrit or of hemoglobin. In all cases leukocytosis involving both myeloid and lymphoid cells occurred. This increase in cells was characterized by mature forms.

3. Since the changes observed were not greater in patients with spleens than in those after splenectomy, they appear not to be due to splenic contraction.

4. It is suggested that a mechanical alteration in the blood stream involving many areas and organs in the body is responsible for the effects observed.

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EXTREME TACHYCARDIA IN THE NEWBORN.

WITH REPORT OF A CASE.

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REPORTS of cases of very rapid heart rates in infants have come from many sources and are not as infrequent as might be supposed. The use of the electrocardiograph has, of course, made it much easier to recognize and classify the disorder and has undoubtedly given impetus to the more frequent submission of reports. No attempt will be made here to review the literature exhaustively since this has been done in several published papers. Those bearing on the points of special interest will be mentioned.

The youngest case on record is that of Werley¹⁷ whose patient

was 4 days old when the condition was recognized. The rate as determined by polygraph was 307 and the child was intensely cyanotic. Death occurred on the 6th day and necropsy failed to reveal any significant cardiac lesions.

Electrocardiographic tracings were obtained in Colgate and McCulloch's³ 2 patients in whom the age at onset of the tachycardia was 21 and 24 days, respectively. The rate in the former was 250 and the latter 291. Both patients were free of symptoms at the time of the report, the first infant having gone 6 months and the second 7 without a recognized attack. No etiology was discovered.

Doxiades⁵ reported the case of a newborn the onset of whose first attack came at the age of 7 days and who had in all 4 episodes of tachycardia, each lasting several days except the last which terminated in 24 hours. The electrocardiogram showed auricular tachycardia. There were no subsequent attacks during 4 months of observation.

In 2 cases cited by von Bernuth,¹⁵ 1 of an infant of 3 weeks and the other of an infant of 2 months, the attacks of tachycardia came on suddenly and were associated with pronounced cyanosis and symptoms resembling shock. In the younger infant improvement after the first attack was followed by recurrence and death. The course in the older child showed no remission. Necropsy revealed in both cases diffuse encephalitis which the author believed was the etiologic factor. In an earlier paper¹⁴ the same author offered 3 cases suggesting widely differing possible etiologies. One of his patients had paroxysmal tachycardia following a toxic myocarditis complicating chorea. A second had attacks "induced by worry" and a third was ill with progressive muscular dystrophy with which the seizures of tachycardia were thought to be associated.

DeBruin's⁴ patient was 5 weeks old and the tachycardia, rate 280, was thought to be due to encephalitis. The patient recovered.

A case of tachycardia associated with congenital heart disease was observed by Schuster and Patterson.¹⁰ Cyanosis and dyspnea had been present from birth but the child was first seen at the age of 2 months. It lived only 2 days longer and had many paroxysms with uncountable pulse, while the interval rate was 180 to 200. Necropsy showed transposition of the great vessels and several anomalous communications between the cardiac chambers.

O'Flynn⁹ presents the case of a child aged 8 months who had two attacks of tachycardia without forewarning, lasting 8 days and 24 hours respectively, and during which the only untoward symptom was anorexia, cyanosis being absent. The cardiac rate during the attacks could not be determined but an electrocardiogram taken after the termination of the second attack showed no abnormalities. Small doses of digitalis had no effect.

Koplik⁷ reported 3 cases: one associated with bronchitis at the onset had repeated paroxysms for two years; another, with a rate

of 240 when seen at the age of 3 years, had had attacks since the age of 6 months, but had never been acutely ill. The writer found digitalis of value in controlling the acute episode but not in preventing its occurrence.

Malossi's⁸ paper contains electrocardiographic tracings illustrating both the onset and the end of a paroxysm. The rate in 1 case, a child aged 6 years, was 240 and in the other, an infant aged 1 year ill with pertussis, was 260. The tracings suggest flutter rather than tachycardia. The child with pertussis had no recurrence of tachycardia after recovery.

The influence of congenital lues as an etiologic factor is discussed by Franke and Weiner⁶ of whose 2 patients one, a boy aged 10, had a positive Wassermann reaction. The other, a girl aged 11, had, as a complication of the tachycardia, ischemic gangrene of both legs for which amputation was necessary. The ischemia was thought to be due to an embolus in the lower aorta which had arisen either from stagnant blood in the auricles (as is seen in auricular fibrillation) or from coexistent vegetative endocarditis.

Willius and Amberg¹⁸ found difficulty in distinguishing between simple tachycardia and auricular flutter in the individual case. Subsequently they¹⁹ reviewed many of the known cases and discussed the criteria for classifying the disorder.

Of 4 cases studied by Shookhoff, Litvak and Matusoff,¹² 3 were thought to be flutter with one to one rhythm. One patient had only two attacks and showed no other findings. Another had the first attack of tachycardia while convalescent from pertussis but has continued to have them since, uninfluenced by medication. The third and fourth cases were associated with myocarditis and congestive failure. Necropsy findings in the last case, presented in detail, show round-cell infiltration, considered a healing infectious myocarditis.

Brown¹ reviews and analyzes a number of cases and reports that of a 3½-year-old child who had had paroxysms every 3 to 4 days from the first year of life. The rate was about 200 and there were no subjective symptoms.

A rhabdomyoma involving the conduction system was found at necropsy on a 10-month-old girl observed by Wegman and Egbert.¹⁶ The patient had had symptoms for several months but the cardiac arrhythmia, believed to be auricular flutter, was noted only on the day of death.

Tatafiore¹³ does not add any new cases but describes the physiologic and pathologic modifications of the heart rate in children.

In 1931 Carr and McClure² described the case of a newborn infant whose apex rate at birth was 180. At the age of 26 hours an electrocardiogram showed auricular flutter. By the tenth day of life the cardiac rhythm was normal and no further abnormalities were noted.

Recently Sherman and Schless¹¹ have recorded the case of a child who was known to have a very high fetal heart rate—about 190, but seemed all right at birth. At the age of 1 month, because of breathing difficulties, roentgenograms of the chest were taken which showed enlargement of the cardiac silhouette. An electrocardiogram at the same time showed auricular flutter with 2:1 block—an auricular rate of 464 and a ventricular rate of 232. At the age of 2 months, because of spells of pallor and weakness, she was admitted to the hospital where similar findings were made. The baby was treated with digitalis and normal rhythm was established and has continued since. They ascribed the disorder to immaturity of the conduction bundle.

The following case is reported as another illustration of benign cardiac arrhythmia in the newborn, where no etiology is apparent.

Case Report. J. C., white male, born May 17, 1933, was admitted to the Pediatric Service of the New Haven Hospital on June 10, 1933, at the age of 24 days, referred by Dr. W. C. McGuire. The chief complaint was heavy breathing and loss of appetite.

The family history was non-contributory; the father aged 33, the mother, 27, and 1 female sibling, 3, were in good health.

The pregnancy had not been abnormal and the delivery was spontaneous, having taken place in a hospital after a labor of 90 minutes. The fetal heart rate varied between 140 and 160. Birth weight was 8 pounds, 2 ounces, and physical examination was reported as negative. At the age of 9 days, when the patient and mother were discharged, he weighed 7 pounds 12 ounces. Breast feedings alone were given.

Nothing untoward was noticed until 5 days before admission when the child began to have 4 or 5 loose stools daily. Beginning at 2 A.M. on the day before admission the baby refused most of his feedings, was breathing heavily and looked ill. The mother noticed that the urine colored the diaper pink. He was given a teaspoonful of milk of magnesia. On the day of admission the patient had a very green stool. A physician who was called ordered a soda enema. However, the child seemed to be growing weaker and the dyspnea more marked so Dr. McGuire was called in consultation. He detected an extremely rapid heart rate and sent the child to the hospital.

The patient was admitted to the accident room at 8 P.M.; at this time his temperature was 36.8° C., and respirations 76 per minute. He was well developed and nourished but was pale and looked gravely ill. The lips were slightly cyanotic and the respirations shallow although the child was crying shrilly. The heart, which did not seem enlarged, was beating with regular rhythm at a rate too rapid to be counted but estimated at 300 per minute. The breath sounds had a prolonged expiratory phase but there were no râles. The liver was definitely enlarged with the edge 3 fingerbreadths below the costal margin and the spleen was down 1½ fingerbreadths. No peripheral edema could be made out.

Laboratory Data: The red blood cell count was not abnormal. The white blood cell count was 24,000 with 34% neutrophils and 64% lymphocytes. The Kahn test, intradermal tuberculin reaction and urinalysis were all negative.

The child was placed in an oxygen tent and his color improved. Pressure on the eyes, vagi, and the abdomen had no effect on the heart rate. At 2 A.M. he was given an hypodermoclysis of 35 cc. saline and 35 cc. 5% glucose solution. At 2.45 A.M. the child was given morphin, gr. $\frac{1}{100}$ and

digifolin, 0.8 cc., equivalent to 0.08 gm. digitalis. No change was observed in the heart within the next hour.

At 10 A.M. the next morning the child looked much better. His temperature was 37.6° C. The heart rate had decreased to 122 per minute and the respirations to 46. The liver had receded to 2 fingerbreadths below the costal margin. A cardiologist, Dr. H. M. Marvin, reported a third heart sound to be present. An attempt to take an electrocardiogram was unsuccessful because of the baby's muscular movements.

The further course was uneventful and the patient gained 225 gm. during his 12-day stay.

Roentgenograms taken on admission show greatly increased hilar markings and similarly increased peripheral markings extending well out into both lung fields. There is no evidence of infiltration or effusion. Films taken the next day, shortly after reestablishment of the normal cardiac rate, show a still greater increase in the markings described above. Further films taken 2 and 10 days later show striking and progressive improvement, the last presenting an essentially normal appearance. In view of the clinical picture the roentgenographic findings are compatible with a diagnosis of passive congestion.

For 3 days at home the child did well but on June 25, 15 days after the first admission, the mother noted rapid respirations and by direct auscultation discerned tachycardia. Pallor but not cyanosis was present. When improvement did not appear in 24 hours the child was brought to the hospital.

SECOND ADMISSION. (Patient 39 days old). The temperature was 37.2° C. and respirations 96 per minute. The heart rate was again too rapid to be counted. The lungs were clear but the liver was enlarged as previously.

An electrocardiogram taken on admission shows a rate of 300 with regular rhythm. The deflections are predominantly downward in Lead I and upward in Lead III—left axis deviation (new terminology). There is a tendency to rhythmic alternation in the size of the *T* wave in Lead I. The configuration is compatible with a diagnosis of either auricular tachycardia or auricular flutter with one to one rhythm (Fig. 1).

Roentgenograms were similar to the first ones taken on the previous admission in showing bilaterally increased pulmonary markings.

Forty-five minutes after admission the infant received 0.08 gm. of digitalis as digifolin subcutaneously along with morphin, gr. $\frac{1}{16}$. Six hours later the child seemed better although still pale; the heart rate was about 120 per minute; respirations 50. Another electrocardiogram at this time showed an essentially normal configuration (Fig. 2).

For the remainder of the 7-day stay in the hospital the heart rate varied from 100 to 130 and nothing unusual occurred. He was discharged July 3, having gained no weight.

Again the baby did well at home but 8 days after discharge he lost his appetite and the mother noted tachycardia. There was neither pallor nor cyanosis. Dr. McGuire was called and gave the patient 2 drops of tincture of digitalis every 4 hours. He received, in all, the equivalent of 75 mg. of digitalis without improvement and admission was advised.

THIRD ADMISSION. (Patient 55 days old). Did not look very ill but was slightly cyanotic. Another electrocardiogram was similar to the first (Fig. 3), but showed more persistent alternation in the size of the *T* wave in all leads. Digitalis, 25 mg., in the form of digifolin, was given immediately and 7 hours later. No change was observed until the next morning when the rate was 120 per minute. Cyanosis was no longer present but the liver was still enlarged. The total amount of digitalis was 125 mg.

Two days later the patient was discharged with the heart rate 120 and the liver again at its average size.

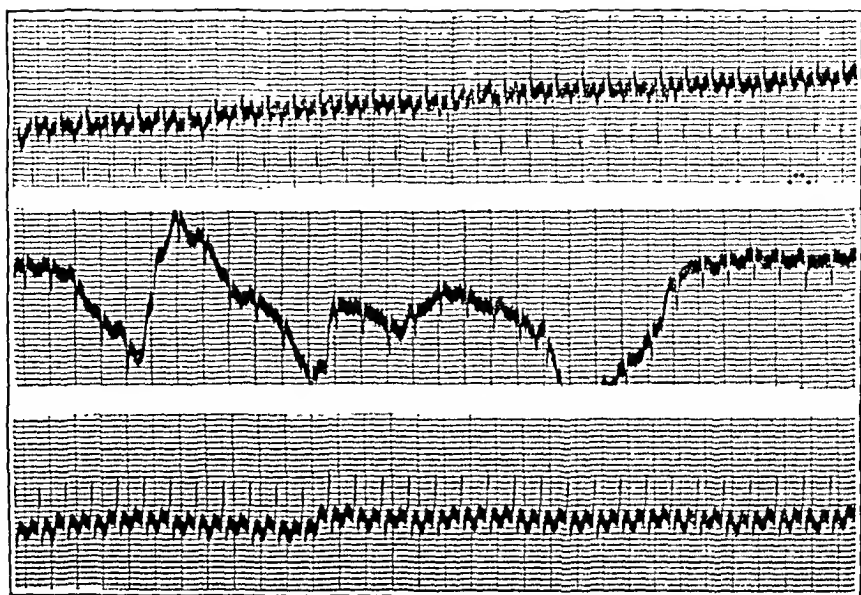


FIG. 1.—Electrocardiogram taken on second admission.

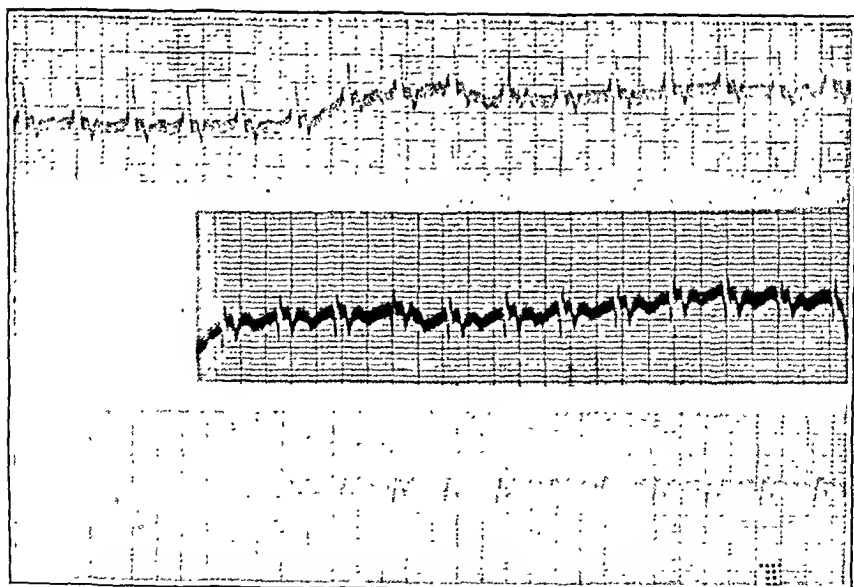


FIG. 2.—Electrocardiogram after resumption of normal rate.

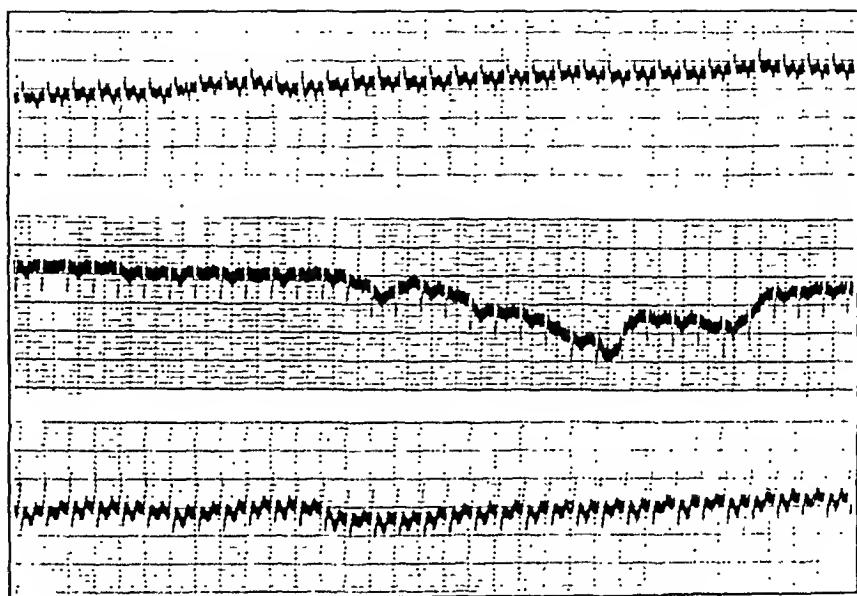


FIG. 3.—Electrocardiogram taken on third admission.

There were no subsequent attacks at home until 3 months after discharge (age 5 months) when the baby became cyanotic during his bath. Although nothing abnormal in the heart was found by the physician the next day the infant was given tincture of digitalis 2 minims 3 times a day for 10 days. About a month and a half after this there was another seizure of tachycardia lasting 3 hours. Two months following this the baby had a very transient paroxysm. Since then he has been free of attacks, has gained weight and developed in a normal fashion.

Discussion. This case presents several unusual aspects. The observations on the fetal heart rate offered an opportunity to detect abnormalities of rate at a time when the latter tends to be high naturally. No such changes were encountered.

Careful observation of the child has failed to give any hint as to what the etiology might be and the decreased frequency and lessened severity of the attacks makes it doubtful if any light will be thrown on this point. The favorable course thus far is compatible with a good prognosis and whatever factors produced the condition acted for a relatively short period and are not now operative.

No treatment that was given during the acute attacks showed any apparent favorable effect on the course of the disease. The symptomatic supportive treatment may have been of greater value than any attempt specifically to influence the heart rate.

The roentgenograms presented a very unusual picture and in the absence of a definite cardiac disorder it would have been difficult to exclude a primary pulmonary lesion. However, we feel justified in assuming that the disturbances in the respiratory system, objectively and subjectively, were a result of the cardiac dysfunction in this instance.

The electrocardiographic tracings do not permit of an accurate distinction between auricular tachycardia and auricular flutter with one to one rhythm. Individual *P* waves may be distinguished but, on the other hand, they may be regarded as part of the flutter cycle which may be discerned if one disregards the ventricular complexes. In an adult the rate would make a diagnosis of flutter almost certain, but when one considers the rapidity with which a normal infant's heart may beat when the child is crying, one must admit that a higher limit ought to be postulated for paroxysmal tachycardia in infants. The significance of the alternation in the size of the *T* wave is also obscure. It has been suggested that such a phenomenon indicates two sources of origin of the heart beat which alternate in the initiation of the excitatory stimulus. There does not seem to be any strong evidence supporting this view. Alternation of the size of the *T* wave with concomitant alternation in size of the *Q-R-S* complex is found in *pulsus alternans*. We do not think the latter condition was present in this case. It is debatable whether any significance should be attached to the failure to react to vagus stimulation.

Conclusion. 1. A case of extreme tachycardia, of unknown etiology, in a very young infant, is presented with roentgenological and electrocardiographic studies.

2. The course of the disorder was not obviously influenced by treatment.

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A STUDY OF THE VALUE OF INSULIN IN UNDERNUTRITION.

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INSULIN has been suggested as a therapeutic agent in a host of non-diabetic conditions. In a discussion of the indications for the use of this drug, Campbell¹ states that "among the thousands of

papers now written on insulin there are some recommending it on quite insufficient grounds for almost every ill to which flesh is heir."

One of the first non-diabetic ailments for which insulin was recommended was malnutrition. In 1923, scarcely a year after insulin was discovered, Pitfield² reported good results using insulin in 2 cases of infantile inanition. In the following year Marriott³ and Barbour⁴ reported marked gains in weight in malnourished infants given glucose and insulin. Falta⁵ in 1925 was the first to describe the use of insulin in cases of adult malnutrition. He states, "beginning with the first experimental day each of the 3 patients studied developed an enormous appetite which increased to actual ravenous hunger with increasing insulin dosage." With this as a beginning a voluminous literature has accumulated in which insulin is enthusiastically recommended for the treatment of undernutrition resulting from most any cause. Its use especially in thin persons without organic disease is advised by Short,⁶ Nichol,⁷ Davidson,⁸ Metz,^{9,10} Barker,¹¹ Blotner^{12,13} and Barron;¹⁴ in malnourished patients with "gastro-intestinal disease or symptoms" by Lueders and Watson;¹⁵ in undernourished tuberculous patients by Arnold,¹⁶ Allen¹⁷ and Heaton,¹⁸ and in psychotic patients by Appel, Farr, and Marshall.^{19,20}

In the large literature dealing with the subject, one seldom encounters an article discouraging the use of insulin in undernutrition. Tisdall *et al.*,²¹ Tezner and Ebel,²² and more recently Radwin and Brown²³ report poor results from the use of insulin in malnourished children. A follow-up study made by Nichol²⁴ showed that relatively few of his insulin treated adult patients maintained the weight they had gained. Wilson, Levine, and Gottschall²⁵ found no fundamental difference in carbohydrate metabolism between normal and marasmic infants, and found no appreciable difference in the amount of carbohydrate burned in infants when they received insulin or when they did not. These workers conclude, therefore, that the use of insulin as a therapeutic agent in marasmic children is not indicated.

The number of satisfactorily controlled investigations of the value of insulin in undernutrition is conspicuously small. Rarely has the effect of insulin been noted separate from that of the improved diet which is simultaneously given. Nor has there been sufficient study of the possibility that benefit observed during the administration of insulin and attributed to this drug, may be largely if not entirely due to a psychic effect.

It is natural then that one might ask the following questions: 1, If insulin causes a gain in weight, is this accomplished through any action of insulin, *per se*, or is it merely by means of suggestion? 2, Is the gain in weight, if it occurs, brought about by increased ingestion of food, or by better assimilation? 3, Is there any consistent relationship between the level of sugar in the blood and the desire for food? 4, How much of the fattening attributed by many authors to insulin is the result of an improved diet and forced

feeding? 5, Might not a patient, aware that he is receiving insulin, eat more food only because he fears hypoglycemic reactions and knows these can be prevented if sufficient food is ingested?

In an attempt to answer these questions, the following study was carried out.

Method. All patients studied were thin persons who complained of poor appetites. Some had no organic disease, others suffered from tuberculosis. Their ages varied from 13 to 44 years. No patients recovering from an acute illness or surgical operation, who ordinarily would have an improving appetite, were studied. Each patient was weighed at frequent intervals under the same conditions (in the morning, before eating or drinking, and after emptying his bladder). The caloric intake of the patient was computed each day. This was done in the following manner. The calorific value of *all* the food presented to the patient during 24 hours was estimated; from this the calorific value of the food not eaten was subtracted; the difference represents his daily caloric intake. Since the same person (a graduate dietitian supervising the therapeutic diets served in the University Hospital) made all these computations, the method is entirely satisfactory for comparative purposes.

The study is divided into two parts.

I.

Plan of Study. During this portion of the investigation no effort was made to fatten the subjects. After observing the caloric intake and weight for a length of time satisfactory to serve as a control period, insulin was injected 30 to 60 minutes (in most cases 45 minutes) before each of the three meals. The patient, however, was not told why he was receiving injections, nor did he know that the medicine was insulin. In fact, special care was taken that the patient have not the slightest suspicion that an appetite response or increased consumption of food was expected. For this reason their general management remained unchanged. The same type of diet and plan of feeding that was used prior to the period of study was continued.* More food was served, however, than the patient had been eating and if at any time still more food was requested, it was generously supplied. These precautions were taken to make certain that the patient would have no difficulty in satisfying his appetite or appeasing his hunger.†

In order to make sure that a sufficient amount of insulin was being given to serve as an adequate test, the dosage was gradually increased from the initial dose of 3 or 5 units until mild hypoglycemic reactions occurred in many patients. Extreme care was taken, however, that no harmful insulin reaction occur. All attend-

* Those who had been receiving only 3 meals a day were similarly served during the experimental period. Those having interval feedings previous to the study continued to receive them.

† Throughout this article, *appetite* is referred to in the sense that Cannon²⁶ uses it to designate a *pleasurable* desire to eat, in contrast to *hunger* which is referred to as a *painful* sensation that experience has shown can be relieved by partaking of food.

ants were instructed to be vigilant for any sign of hypoglycemia, and should a reaction occur, to treat it at once.

Using this procedure, the possibility of the patient increasing his consumption of food in order to prevent hypoglycemic reactions was eliminated, and an increase in one's desire for food as a result of insulin might be observed unassociated with any psychic effect.

TABLE 1.—THE RESULTS OF ADMINISTRATION OF INSULIN TO THIN PATIENTS WHO DID NOT KNOW THEY WERE RECEIVING INSULIN OR THAT AN INCREASE IN APPETITE OR HUNGER WAS EXPECTED TO ACCOMPANY THE INJECTIONS.

Patient.	Age.	Sex.	Diagnosis.	Length of time insulin was administered.	Dosage of insulin at time injections were stopped.	Hypoglycemic reactions.	Total change in weight while receiving insulin.	Average daily caloric intake while receiving insulin.	Appetite or hunger.
				(Days.)	(Units.)			(Calories.)	
H. S.	21	M	Pulmonary tuberculosis and tuberculosis of hip (afebrile)	19	10-10-10	None	Lost 1.2 kg.	1880 (No change during insulin period)	Reported no change.
J. M.	18	M	Pulmonary tuberculosis (minimal) (afebrile)	17	7-7-7	On 2 occasions	Gained 0.6 kg. (same rate of gain prior to insulin)	1863 (No change while receiving insulin)	No improvement in appetite; hunger did not accompany hypoglycemia.
J. J. M.	19	M	Pulmonary tuberculosis (afebrile)	45	16-16-16	Gained 1.2 kg. (less than rate of gain prior to insulin)	2110 (Less than before and after insulin)	No change.
L. D.	39	F	Pulmonary tuberculosis (afebrile)	26	8-8-8	3 definite reactions	Lost 0.4 kg. (gained 2.3 kg. in 45 days after insulin was stopped)	1289 (1525 after insulin was stopped)	No change; not hungry during insulin reaction.
M. A.	29	F	Psychoneurosis	18	20-20-20	1 moderately severe	Lost 0.6 kg.	1074 (1111 after insulin was stopped)	No change.
F. W.	19	F	Psychoneurosis	10	15-15-15	1	Lost 0.7 kg.	721 (863 after insulin was stopped)	No change; not hungry during insulin reaction.
J. W.	19	M	Pulmonary tuberculosis	14	6-6-6	None	Lost 0.2 kg.	2351 (No change during insulin)	No change.
S. P.	18	M	Pulmonary tuberculosis (afebrile)	18	9-9-9	None	Gained 2.1 kg. (gained 1.7 kg. during 17 days prior to insulin)	2970 (2590 prior to insulin)	"Appetite improving."
T. J.	31	M	Psychoneurosis	8	15-10-10	Gained 2.5 kg. (gained 2.2 kg. in 4 days prior to insulin)	3200	"Good appetite."

Results. In this way the effect of insulin was observed in 9 patients. A summary of the results is shown in Table 1. Of the 9 subjects studied, 7 had no increase in appetite, food consumption, or rate of gain in weight. Five of these 7 actually lost weight during the administration of insulin. Two gained weight; J. M. at a rate equal to the gain prior to insulin therapy, and J. J. M. at a rate

slower than during the period before insulin was given. The table shows the continued low calorie intake in these 7 patients. Patient S. P. gained weight at a rate slightly more rapid than before insulin was given, and his calorie intake was noticeably increased. He felt that his appetite was improved. Patient T. J. gained 2.5 kg. in the 8-day period during which he received insulin, but it should be noted that during the 4 days just before insulin was administered he gained 2.2 kg.

II.

Plan of Study. In the second part of this study an attempt was made to fatten the subjects, and to measure separately the effect of (1) a high caloric diet, (2) suggestion accompanying injections, and (3) insulin. In this way, it would be possible to determine whether or not insulin, by reason of any pharmacologic effect, is a therapeutic aid in fattening thin persons.

To accomplish this purpose the following procedure was adopted: A high caloric diet was instituted. For control purposes, a diet identical day after day throughout the study would be desirable, but because the monotony of this might cause a decrease in appetite, the patients were given their choice of food rich in energy for three meals a day, and in addition high calorie interval nourishments were served. Each patient was served more food than he had been eating previously. Additional food was supplied at any time the patient wished it. Thus the patient could eat all he desired. This dietary and manner of feeding remained unchanged throughout the entire period of study.

The calorie intake and changes in weight were observed for a control period (usually 2 or 3 weeks) after starting this diet. Subsequently, injections were given 30 to 60 minutes (usually 45 minutes) before each of the 3 main meals. When the injections were started the patient was enthusiastically told that he was being given these injections because there was reason to believe they would whet his appetite, make him hungry, and thus increase his consumption of food and improve his state of wellbeing. However, in order to determine how much psychic effect was produced, sterile water or saline was injected for a period of 2 or 3 weeks. Then, at a time unknown to the patient, insulin in increasing doses was substituted for the placebo. The dose of insulin was increased in almost every instance until one of the following effects was noted: (1) until an improvement of appetite or hunger was noted and reflected by increased consumption of food and rate of gain in weight, (2) until any undesirable reaction from insulin was noted, or (3) until the noon blood sugar was recorded at a low level (see below). So, although the patient knew an improvement of appetite and increased food consumption were expected, he did not know when insulin

was being injected. The same care to avoid harmful reactions from insulin was exercised.

During the period when insulin was being given, frequent sugar determinations, by the method of Folin-Wu,²⁷ were made on blood obtained at 12 o'clock noon, just before the patient began his mid-day meal. In this way, it was hoped to learn whether or not any increased desire for food resultant from insulin need be associated with hypoglycemia. A noon blood-sugar determination was made at the beginning of the study to serve as a control.

Results. The results of the second portion of this study can best be shown graphically. The accompanying figures (1 through 8) show the response in 8 of the 11 individuals studied in this way.

Explanation of Graphs. The age, sex, and diagnosis of the patient appear on each graph. I. W. represents the "ideal weight"* in each case. The patient's weight and daily caloric intake are plotted on the upper and middle third of each graph, respectively; in the lower third the total daily insulin dosage (I) is shown by a line and the noon blood-sugar level (B. S.) represented by a cross (X). Insulin reactions are indicated by an R in the portion of the graph where insulin is plotted. In some cases the weight record prior to the period of study is shown. Each graph is divided into panels showing the response to (1) diet only, (2) to the same diet plus sterile water (S. W.) or sterile saline (S. S.), and (3) to the same diet plus insulin. The numbers in the weight and caloric intake spaces indicate the average daily weight change in grams, and the average daily caloric intake in each case. The average daily caloric intake for the different periods is also represented graphically.

Clinical Data. Two patients, one a girl, A. B., aged 13, with renal and pulmonary tuberculosis (afebrile), the other a boy, I. M., aged 14, having widespread pulmonary tuberculosis (afebrile) both markedly undernourished and having poor appetites failed to respond in any way to diet, placebo, or insulin, even though the latter was given in doses sufficiently large to cause mild hypoglycemic reactions in each case, and to lower the noon blood sugar to 44 mg. % in the girl and to 55 mg. % in the boy. There was no subjective improvement in either patient. Since the response is practically identical in each case, a graph is shown for only the girl (Fig. 1).

Figure 2 shows the response of Miss C. W. There was a beneficial response to the increased diet, a slight additional improvement when a placebo was given, and a falling off of caloric intake and decreasing rate of gain during administration of insulin. There was no subjective response accompanying the administration of insulin.

Miss M. B. (Fig. 3) was benefited by the diet alone. Added benefit occurred when placebos were given. When insulin was used there was no significant change. This patient reported that her appetite was better as soon as she began receiving placebos. The first day she received 13 units of insulin before each meal she said she felt hungry before breakfast, but on that day the caloric intake did not change significantly.

Observations made on Miss L. P. are shown in Figure 4. Again, a distinct improvement resulted from feeding a high caloric diet, and an unques-

* "Ideal weight" here refers to the *average* weight for a normal individual of the patient's sex, age and height.

tionable additional benefit from placebos. An actual decrease both in caloric intake and rate of gain occurred when insulin was administered. This patient stated that her desire for food seemed greater when she began receiving placebos. At no time during the administration of insulin did she report any subjective change.

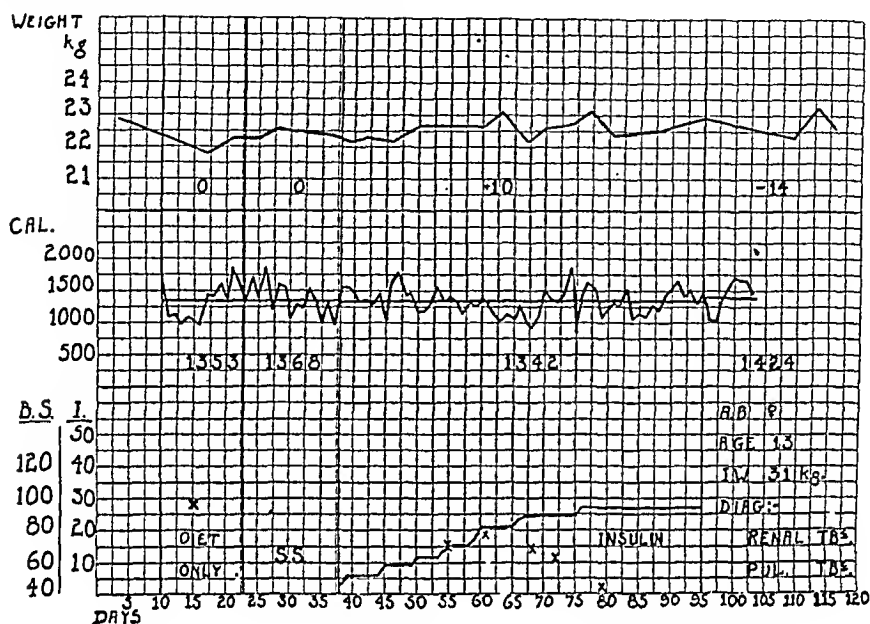


FIG. 1

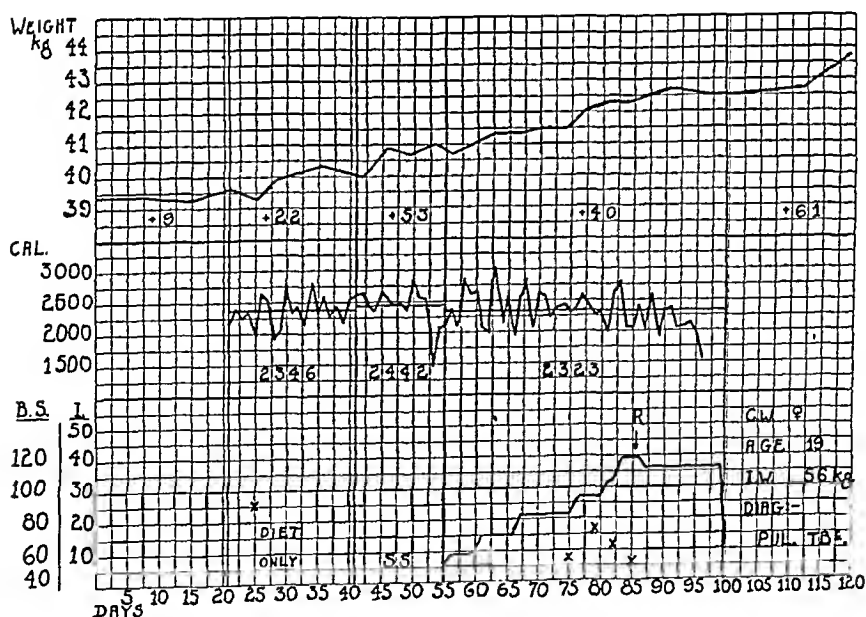


FIG. 2

When studying Miss V. H. (Fig. 5) a slight variation in procedure was made. After demonstrating a slight gain in weight on the diet alone, place-

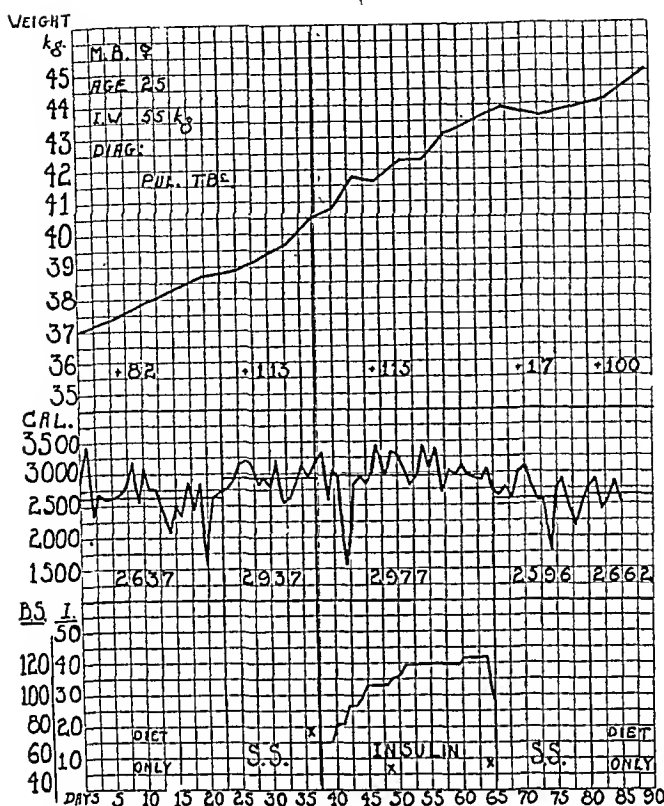


FIG. 3

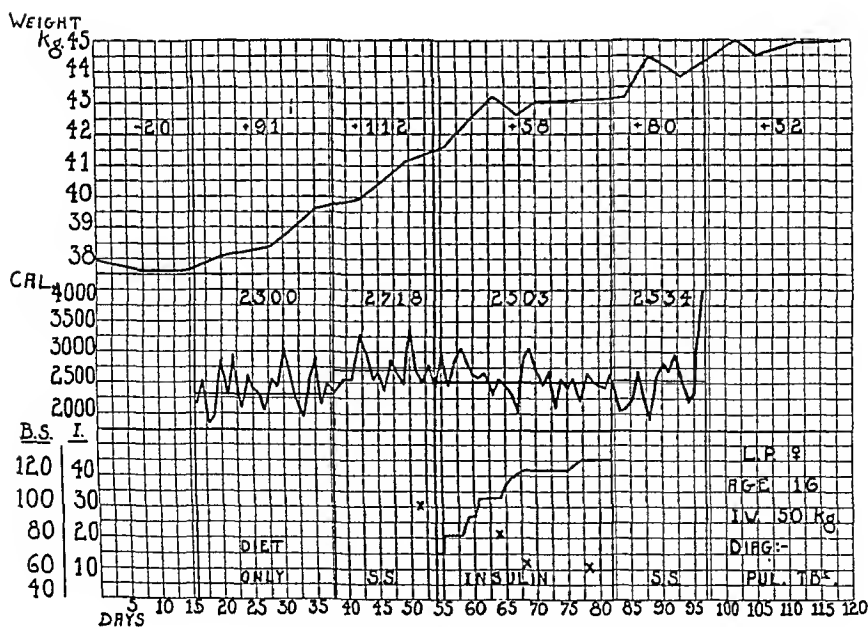


FIG. 4

bos were given. When these were started the patient was not told why the injections were being given. There was a falling off of the caloric intake. The patient was then told that these injections were given to increase her desire for food. She promptly reported an improved appetite and her food consumption increased noticeably so that the average daily caloric intake was decidedly higher than it was during the period of high caloric diet alone. When insulin was substituted no significant change in caloric intake occurred. She reported a feeling of *hunger* at times just prior to meals, when the insulin dosage was high. No appetite change accompanied the use of insulin in this patient. She disliked all injections.

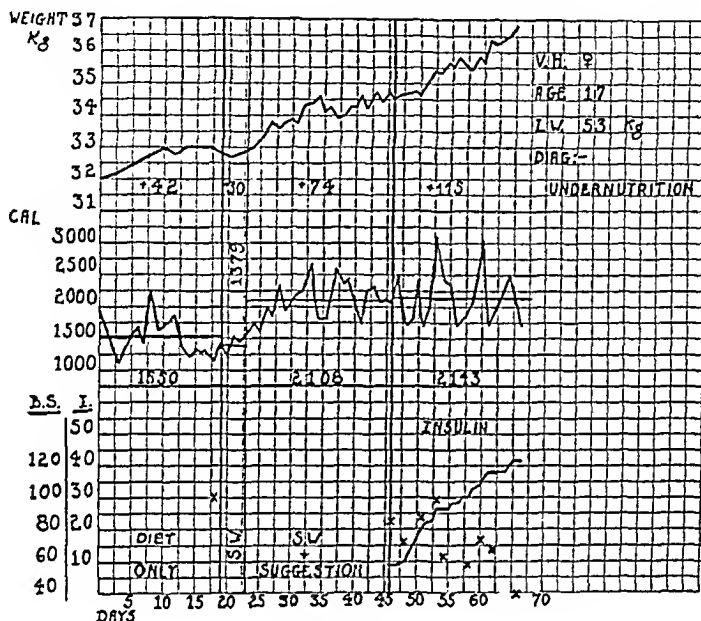


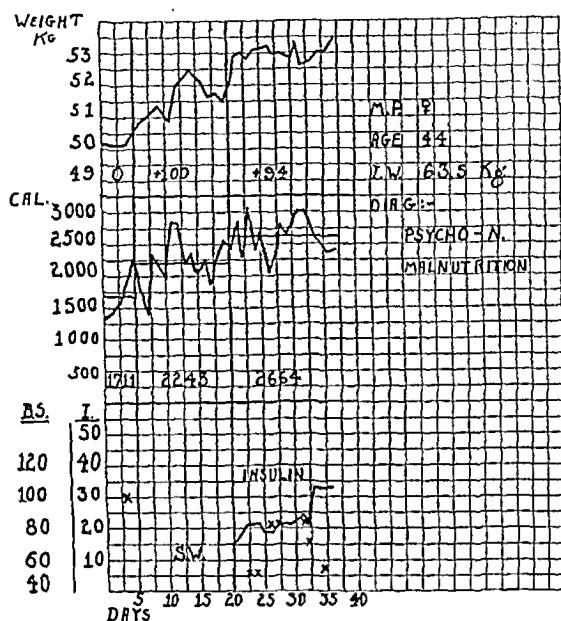
FIG. 5

Mrs. M. P. (Fig. 6) was distinctly benefited by the administration of placebos. There was an additional increased consumption of food during the period when insulin was given. Because of her neurosis, subjective change could not be evaluated in this patient.

A 17-year-old girl, Miss D. G. (Fig. 7), responded well to the improved diet. She, however, greatly disliked injections, and showed a decreased food intake and stationary weight when normal saline was injected. When insulin was begun there was a prompt lowering of blood sugar and the patient reported having a feeling of hunger prior to the morning and noon meals, and a good appetite for all meals. Unfortunately figures for her caloric intake during the early part of the insulin period have been lost; nevertheless, the weight curve shows prompt gain in weight, and the average caloric intake over the latter part of this period shows distinct increase in food consumption. It should be noted, however, that the average daily caloric intake and gain in weight are essentially the same as when she received the high caloric diet alone. The prompt lowering of caloric intake when insulin was stopped and placebos substituted suggest, however, that insulin might have been of benefit to this patient.

One of the most interesting patients studied was Mr. R. R. The data in his case over the long period of study are shown in Figure 8. Diet alone

was not successful in fattening this patient. When placebos were given a slight benefit resulted. A decided additional advantage was noted when insulin was injected. The patient stated that he had a better appetite and frequently felt hungry before meals when insulin was given. Subjective and objective improvement ceased when sterile water was substituted for insulin. After these observations were made it was decided to carry out



F Fig. 6

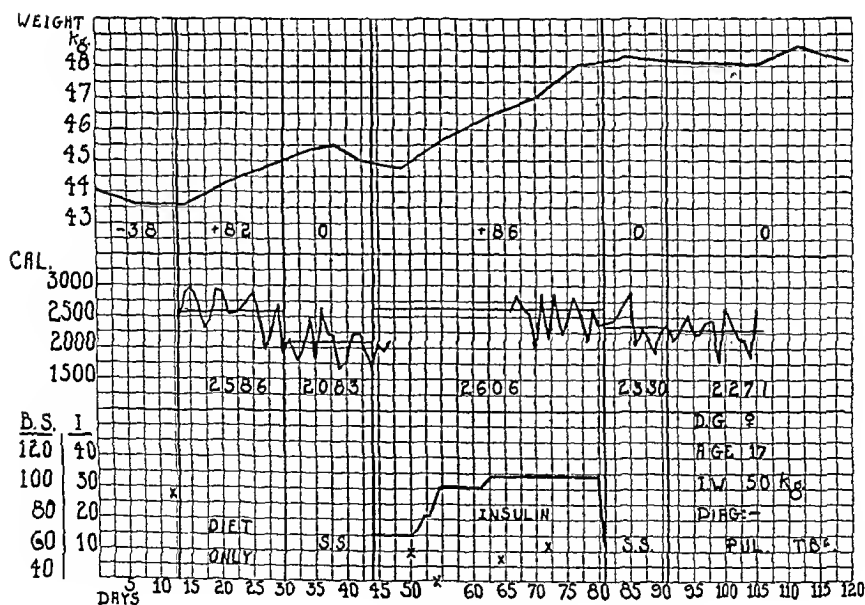


Fig. 7

the same study again on this patient. Accordingly, after another control period of diet alone, sterile water was again injected. There was a repetition of the slight benefit previously noted with the administration of placebos. Interestingly enough, however, when insulin was given the second time no increase in caloric intake occurred, and the weight curve did not change. (The average daily gain in weight as calculated is greater, but it so happens that both at the beginning and at the end of the period the fluctuations normally occurring in one's weight were such to produce this erroneous figure. Inspection of the weight curve from the 80th to the 155th day shows it to follow a straight line.) There was no subjective change during this second period of insulin. This lack of response is the more interesting when it is seen that the noon blood-sugar levels during the second insulin period were lower than during the first insulin period, and that the patient's weight is still far below his "ideal weight."

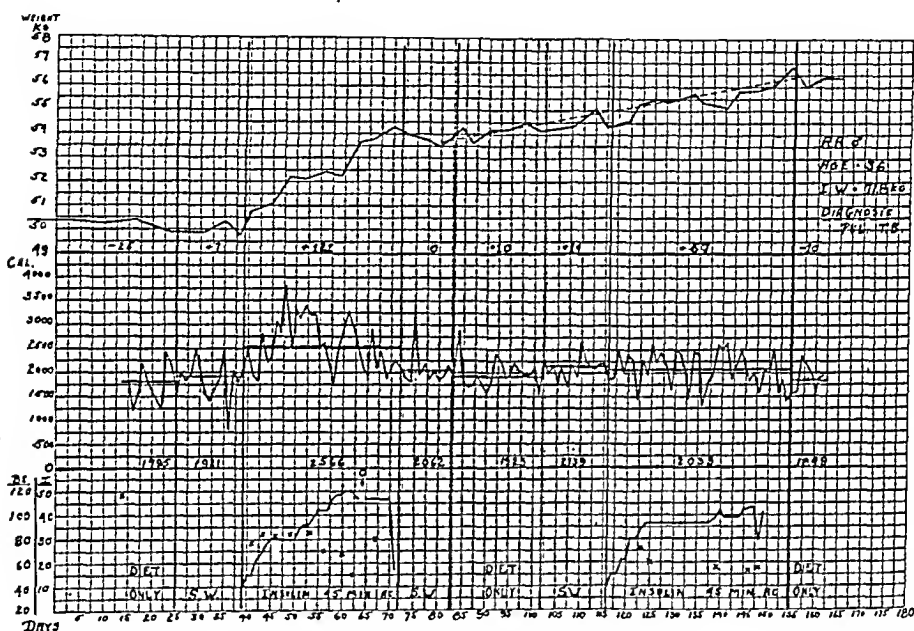


FIG. 8

Charts are not reproduced for the last 2 patients studied. Mrs. E. H., aged 41, who had chronic arthritis, and latent lues, was 19 kg. under her "ideal weight." She gained nicely on the diet alone. Her average consumption was 2643 calories daily. During the time she received sterile saline, she consumed an average of 2872 calories daily with a corresponding increase in gain in weight. During the short time she was receiving insulin (5 days), but in amounts sufficient to lower the noon blood sugar to 56 mg. %, she consumed an average of 2875 calories and gained weight at a rate slightly less than when receiving placebos. There was no important subjective change in her case.

The last patient studied, Miss D. R., aged 22, whose diagnoses were psychoneurosis and malnutrition, weighed only 27.4 kg. Her "ideal weight" was 50 kg. On the diet she gained only slightly. She objected severely when injections of sterile water were started and seemed to revolt against eating. Her average daily caloric intake fell from 1580 to 926. When insulin was given the average daily consumption was only 819 calories.

Insulin, which was started in 3 unit doses and increased to 8 units t.i.d., was stopped after 8 days because of her continued objection to injections even though she understood they were given in an attempt to improve her appetite. On the day insulin was stopped, a 5% glucose solution was given intravenously because her food consumption was so small. She disliked the intravenous therapy sufficiently that in order to avoid being given more infusions, the very next day she consumed 2100 calories and maintained an average daily intake of 2157 calories for the remainder of her stay in the hospital. She gained weight correspondingly.

A summary of the results of the second part of the investigation appears in Table 2.

TABLE 2.*—RESULTS OF ATTEMPT TO FATTEN PATIENTS FIRST WITH A HIGH CALORIC DIET, NEXT WITH DIET AND PLACEBO, AND LASTLY WITH DIET AND INSULIN.

Patient.	Benefit from high caloric diet only.			Additional effect of placebo.				Additional effect of insulin as compared with diet plus placebo.			
	None.	Slight.	Good.	Worse.	No change.	Benefit.		Worse.	No change.	Benefit.	
						Slight.	Good.			Slight.	Good.
A. B. . . .	+	+	+		
I. M. . . .	+	+	+		
C. W.	+	+	..	Slightly			
M. B.	+	+		+		
L. P.	+	+		+		
V. H.	+	+	..	+		
M. P. . . .	+	+	+
D. G.	+	+	+
R. R. . . .	+	+	+
(Repeat) . .	+	+	+	..	+
E. H.	+	+	+		
D. R.	+	..	+	+		
Total† . .	4	3	4	2	2	3	4	2	6	0	3

* This table is based primarily on a comparison of the daily caloric intake, with which the changes in weight very closely agree.

† Excluding repeat study in R. R.

Discussion. The results of this study do not substantiate the claim that insulin is a valuable adjunct in the treatment of undernutrition. No appreciable benefit occurred in 8 of the 9 patients first studied, who were injected with insulin without their knowing what medicine was being given or why it was administered. Mr. S. P. was the only subject in the first group who showed an increased rate of gain in weight when insulin was administered, and it should be noted that prior to insulin therapy he consumed enough food to cause him to gain weight at the rate of 100 gm. a day. Only 3 of the 11 subjects of the second part of the study showed a response that might be attributed to insulin. In 1 of these 3 patients, Miss D. G., the response to insulin was decidedly better than that to a placebo, but no better than the response to the high calorie diet alone; and

in another, Mr. R. R., the very definite improvement noticed when insulin was first administered did not occur during the second period of insulin therapy. In 6 patients of the second group there was no significant change in caloric intake or weight when insulin was substituted for a placebo, and in 2 the benefit was actually less when insulin replaced the placebo. Only 2 patients of the entire study then showed any improvement that could certainly be attributed to insulin. No patient showed remarkable improvement during the administration of insulin and ravenous hunger reported by so many writers was not once observed.

One wonders how insulin might be beneficial, if it is, when administered to undernourished patients. Okada *et al.*²⁸ have shown that the injection of insulin increases gastric, biliary and pancreatic secretions. Lueders and Watson¹⁵ measured an increase in concentration of pancreatic ferments recovered from malnourished patients when insulin was given. These authors felt that the patient's gain in weight was due in part to an improvement in digestion and assimilation of food elements which resulted from the increased concentration of pancreatic enzymes and bile. The fact that there is such close correlation between the caloric intake (ingestion) and changes in weight of the patients herein reported shows that during insulin therapy there certainly was no important increase in absorption or utilization of food, but rather that the digestion, absorption and metabolism of food remained unaffected, and whatever increase in weight that occurred during the administration of insulin resulted from increased ingestion.

Bulatao and Carlson²⁹ found that when insulin is injected into normal dogs, "gastric hunger contractions and gastric tonus are augmented to the point of incomplete gastric tetany when the blood sugar falls to 0.085 to 0.075 mg. %." Later, Quigley, Johnson, and Solomon³¹ reported that when normal fasting human subjects were injected with 12 to 20 units of insulin an increase in gastric tonus and hunger contractions, and a prolonged hunger period resulted. They suggest that it may be this effect of insulin on the stomach which leads to an increased ingestion of food that accounts for the gain in weight accompanying the administration of insulin to persons with anorexia. The results obtained in this study conform to this view. The close correlation between changes in weight and caloric intake, and the subjective sensation of hunger, when the dosage of insulin was sufficient to cause a distinct fall in blood sugar, surely favor this explanation for the beneficial effect of insulin when it occurs. Because this response occurred in the minority of patients studied and because reactions to insulin were frequently observed without an accompanying sensation of hunger it appears that this effect of insulin does not uniformly occur, or may be present for such a short time that it is ineffectual as a stimulus to increase food consumption.

That there is undoubtedly an important psychic factor in many of the patients to whom injections were given is demonstrated by this study. There was a decided lack of beneficial effect of insulin when it was given to patients ignorant of the nature of the medication and the results expected. On the other hand, definite improvement was noted subjectively and objectively in several of the patients expecting benefit from injections when the substance injected was only sterile saline or water. There can be no doubt that the improvement which accompanied the injections of saline in patients M. B., L. P., V. H., and M. P. would have been attributed to insulin had this drug been injected without a preliminary control period of saline injection. There has been insufficient evaluation of this psychic effect, which is often great, and which may in some cases account for the entire improvement noted.

That benefit commonly credited to insulin belongs in part to concurrent improvements of the dietary is amply shown in the latter half of this study.

Conclusions. 1. This investigation fails to support the prevalent opinion that insulin is a valuable aid in the treatment of undernutrition.

2. When undernourished patients were injected with insulin and its effect noted separately from diet and suggestion the great majority of patients failed to show any response. The improvement which was attributable to insulin in 2 cases was small.

3. The fact that improvement resulted in many patients from the *suggestion* accompanying injections, indicates that much of the benefit commonly attributed to insulin is due to a psychic factor.

The author is deeply indebted to Dr. L. H. Newburgh for many helpful suggestions made during the progress of this investigation, to Miss Mary Stanley for the blood-sugar determinations, and to Miss Gladys Enke for computing the daily caloric intake of the patients studied.

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- (Titles have been omitted for sake of brevity.)

FULMINATING HEMORRHAGIC ENCEPHALITIS.

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In the numerous papers on encephalitis published during the past few years, little or no mention has been made of the rapid and fatal course the disease may take. It is the purpose of this communication to call attention to the fulminating type of encephalitis which terminates in unexpected and sudden death.

The clinical histories and autopsy findings of 5 cases of encephalitis are recorded. Unusual features, and the justification of the term "fulminating" encephalitis, are emphasized.

In every instance an autopsy was performed a few hours after death. The brain was preserved in formalin for 2 weeks before it was examined. Sections of the brain taken from various portions were stained with hematoxylin and eosin. Davenport's method was used for the study of the axis cylinders, the Weil method for the staining of the myelin sheaths, and Holzer's stain for the study of glia fibers. The von Gieson stain was used when deemed necessary.

Case Abstracts. CASE 1.—A white male infant, aged 4 months, was perfectly well until the day of his death. On that day, while out with his nurse, he developed signs of dyspnea as if he had inhaled a foreign body.

He was hurried home and a pulmotor squad was called, but he became markedly cyanotic and died.

Necropsy revealed a well-developed and well-nourished infant. The lymph nodes, particularly the mediastinal and peritoneal, were larger than normal. The follicles and Peyer's patches throughout the gastro-intestinal tract were hyperplastic. The thymus weighed 55 gm. Both lungs revealed a very recent bronchopneumonia. The aorta was hypoplastic. There were 3 accessory spleens. The brain was markedly hyperemic. On section, the white and gray substances appeared reddish, and petechial hemorrhages were found throughout the white substance. Hemorrhages were also noted in the pons and cerebellum.

Histologic examination of the brain revealed a marked dilatation of the smaller vessels, which were packed with red blood corpuscles. Many perivascular spaces contained red blood corpuscles. Extravasation of these cells was more pronounced in the region of the third and fourth ventricles. Lymphocytes and a few neutrophils were also found in the perivascular spaces.

The *anatomic diagnosis* was acute catarrhal bronchitis; recent bilateral bronchopneumonia; very early acute hemorrhagic encephalitis; enlarged thymus; generalized lymphoid hyperplasia; marked hyperplasia of the follicles and Peyer's patches of the gastro-intestinal tract; three accessory spleens.

Summary of Case 1. Inasmuch as the autopsy revealed a marked increase in the lymphadenoid tissue throughout the body, as well as a large thymus, it is possible that this child belonged to the group classified as status thymico-lymphaticus. This may explain the lowered resistance of the child and the reason he succumbed so rapidly to the acute infectious disease. We shall return to this later. The cause of death, in our opinion, was an acute hemorrhagic encephalitis, with the recent bronchitis and bronchopneumonia as the portal of entry of the etiologic agent. In other words, the child, whose resistance had been low since birth, developed bronchitis and bronchopneumonia and an acute inflammation of the brain from which he died.

CASE 2.—A white female child, aged 29 months, was admitted in a moribund state. Three hours prior to admission the patient's parents heard her calling and found her in convulsions. The temperature was 107°. The child was rushed to the hospital. Diffuse clonic convulsive movements of all extremities were present. The neck was rigid and the pupils were fixed and dilated. The skin was covered with purplish-red blotches. The temperature on admission was 106°. A lumbar puncture yielded 20 cc. of a clear, colorless fluid. The fluid contained 11 white blood cells, 5 of which were neutrophils and 6 lymphocytes. One hundred and fifty red blood cells were present. The Pandy test was negative. The sugar content of the cerebrospinal fluid was 85 mg. per 100 cc.

The child had previously been well. She had had no symptoms of a cold, sore throat or other ailment prior to the onset of the disease.

The course was steadily downhill. The child did not improve following the administration of sedatives and died 1½ hours after admission to the hospital.

Necropsy revealed a recent bronchopneumonia in portions distinctly hemorrhagic. The aorta was hypoplastic. There was a fatty metamorphosis of the liver and a cloudy swelling of the kidneys. The follicles of the

spleen were very prominent. The thymus weighed 65 gm. and revealed minute hemorrhages. The Peyer's patches and the lymph follicles in the small and large intestines were very prominent. The cortical vessels were markedly hyperemic. The gyri were flattened and swollen and the sulci were narrowed. On section, the white substance of the brain was pinkish and its differentiation from the cortex indistinct. Many petechial hemorrhages and dilated capillaries were seen throughout the white substance of the brain.

The *histologic examination* of the lungs revealed some alveoli filled with neutrophils, mononuclear and red blood cells and phagocytic cells containing brown pigment granules. The Gram-Weigert stain revealed the presence of bacteria arranged in groups of two.

Sections of the brain showed, in many places, a distinct extravasation of red blood corpuscles into the perivascular spaces. Occasionally a few neutrophils were found in these spaces, as were a number of lymphocytes. Some of the fields revealed red blood corpuscles in the parenchyma, apparently not in the vicinity of the vessels. Many ganglion cells had markedly faded nuclei and in many instances, nuclei were not recognizable.

Summary of Case 2. The outstanding feature of this case is the very short duration of the illness, which lasted only about 6 hours. The cause of death was a very acute hemorrhagic encephalitis. The bronchopneumonia was apparently of longer duration than the encephalitis. Sections of the lungs contained diplococci. Bacteria were not found in the brain.

CASE 3.—The essential points in the history of this white male child aged 9 months, were a cough which had persisted for 3 days, convulsions which had begun 10 hours before admission, drowsiness, heavy breathing, stridor, generalized rash and cyanosis of 10 hours' duration. Except for the cough, the child had been well until the day before admission to the hospital, when he had refused to eat.

On admission, the child was acutely ill. There was marked inspiratory stridor. The patient's temperature was 105.8°, pulse 160, respirations 58. His pupils were fixed and there were petechiæ in the conjunctivæ. The right ear drum was red, the pharynx hyperemic and the tonsils were enlarged. The neck was not rigid. The heart was normal. There was a marked sternal retraction during inspiration. Bronchial breathing could be heard over the right lung, as could crepitant râles on both sides; all sounds, however, were obscured by the inspiratory stridor. Petechiæ were present over the face, neck, chest and extremities. The face and extremities were cyanotic.

The impression on admission was bilateral bronchopneumonia; toxemia, secondary purpura; probable encephalitis.

The child was put into an oxygen tent. His respiration and pulse became more rapid and he died 2 hours after admission to the hospital. No laboratory work was done.

Necropsy revealed a bilateral bronchopneumonia. The lymph nodes throughout the body and the solitary follicles and Peyer's patches in the gastro-intestinal tract, were enlarged and hyperemic. The thymus weighed 45 gm. There were petechial hemorrhages in the pleuræ, pericardium, intestinal mucosa, bladder, pelvis and skin. The brain was markedly hyperemic and minute petechial hemorrhages were seen throughout the white substance, especially in the region of the left basal ganglia. Petechiæ were also seen in the left dentate nucleus. There was slight hemorrhage in both suprarenals.



FIG. 1

FIG. 1.—Case 1. Early acute hemorrhagic encephalitis. Note the hemorrhages in the perivascular spaces. Hematoxylin and eosin. (150 X.)



FIG. 2

FIG. 2.—Case 1. Note the perivascular infiltration. Hematoxylin and eosin. (180 X.)

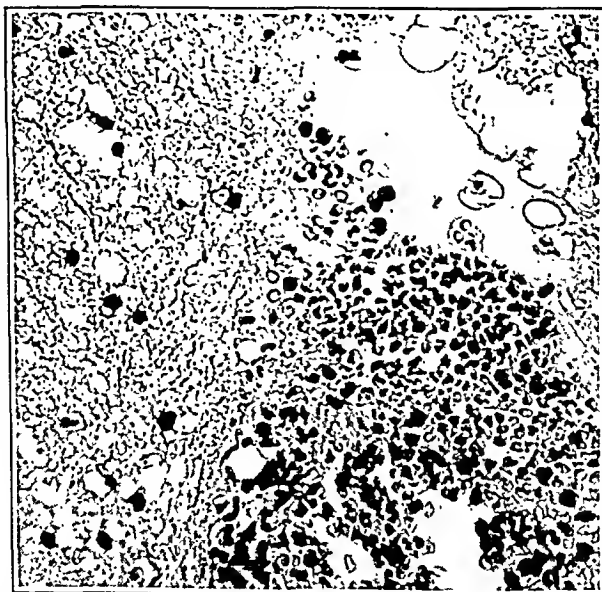


FIG. 3.—Case 2. Note the red cells with a few neutrophils free in the tissue. Hematoxylin and eosin. (380 X.)

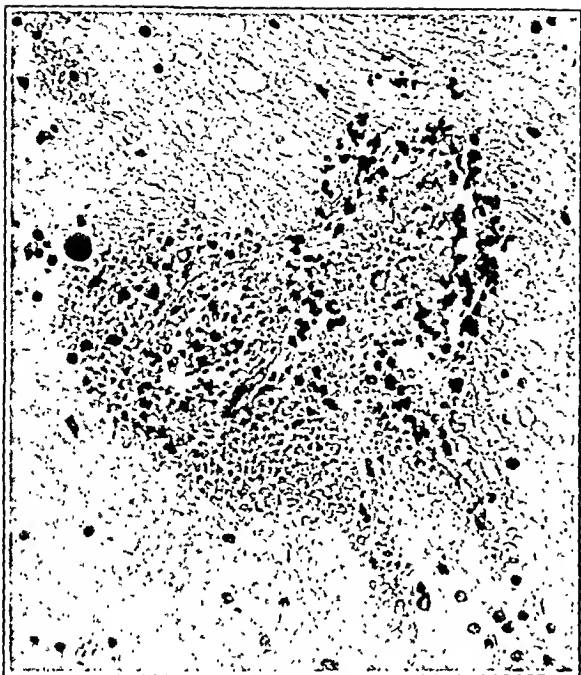


FIG. 4

FIG. 4.—Case 3. Note the hemorrhage and the neutrophils. Hematoxylin and eosin. (260 \times .)



FIG. 5

FIG. 5.—Case 5. Note the perivascular infiltration of neutrophils. Iron-hematoxylin and eosin. (240 \times .)

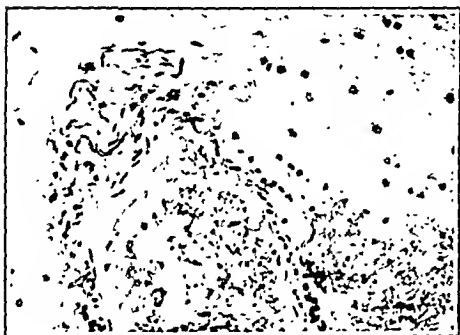


FIG. 6

FIG. 6.—Case 5. Perivascular infiltration of neutrophils and perivascular hemorrhage. Iron hematoxylin and eosin. (180 \times .)

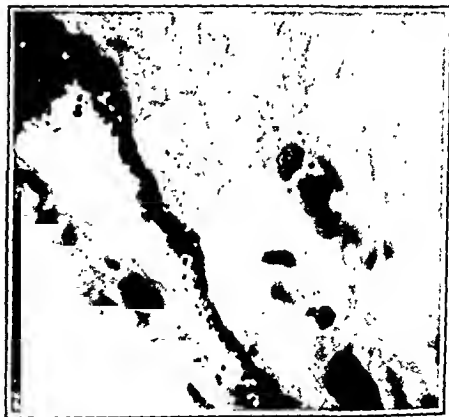


FIG. 7

FIG. 7.—Case 5.—Cocci with the blood vessel and wall. Gram Weigert. (600 \times .)

Microscopic section through the brain revealed the following histologic changes: The large and small bloodvessels, particularly the capillaries, were distended with red blood corpuscles; many red cells were found free in the perivascular spaces. In places, some of the small bloodvessels were surrounded by lymphocytes and only very occasionally were neutrophils found. Minute accumulations of lymphocytes were seen throughout the cortical portions of the brain. The ganglion cells showed a marked granularity of their cytoplasm and in many instances the nuclei were absent.

Summary of Case 3. The chief interest of this case lies in the short duration of the illness. As has been mentioned above, the child felt fairly well until the evening preceding his admission to the hospital, when he suddenly became drowsy. He died the day he was admitted to the hospital. The cause of death was acute encephalitis.

CASE 4.—A white female, four and a half years of age, had been well until she contracted whooping cough, which had lasted 2 weeks and was relatively mild. She ate and slept fairly well until 24 hours before admission to the hospital, when her mother noticed that she was restless during the night and seemed apathetic. The next day, the child's face seemed asymmetrical.

Physical examination after admission to the hospital revealed a right facial paresis and weakness of the right leg. The patient was rational. The following morning, about 30 hours after the onset of the illness, she had clonic and tonic convulsions and was unable to talk. Definite paralysis of the right side was noticed at that time. There was but a slight elevation of temperature during the period of hospitalization, not higher than 100.4° rectally. The urine contained glucose and a trace of albumin.

The child died 48 hours after the onset of the symptoms, with signs of respiratory paralysis. A spinal puncture, performed the day the convulsions occurred, yielded clear fluid under increased pressure, with but 5 cells per c.mm.

Necropsy (confined to the brain). The brain was markedly hyperemic. Petechial hemorrhages were found in the region of the frontal lobe. Minute hemorrhages were found throughout the cut sections of the brain; these were more pronounced in the region of the left orbital and frontal lobes. The subarachnoid space contained a small amount of serous liquid.

On *histologic examination*, neutrophils and a few lymphocytes and endothelial cells were found in the subarachnoid space. About the bloodvessels within the brain tissue was found a network of homogeneous pink-staining material, in the meshes of which were red blood corpuscles, neutrophils, endothelial cells, lymphocytes, and nuclear debris. Foci of neutrophils, lymphocytes and endothelial cells, in addition to accumulations of red cells, were also found within the brain, but not in relation to bloodvessels.

Summary of Case 4. Because of the more severe involvement of the brain than of the meninges, we are of the opinion that the encephalitis was primary and the meningeal reaction secondary.

CASE 5.—A 37-year-old white male was admitted to the hospital at an early morning hour and died the same day. The patient was apparently well previous to the onset of his illness. At midnight, he had been awakened by his wife and asked to attend to their child, who had whooping cough. He was apparently rational at the time and went back to bed. At 1.45 A.M., his wife was awakened by his stertorous breathing. She was unable to rouse him. On admission to the hospital, the patient was in deep coma,

with Cheyne-Stokes respiration and generalized cyanosis. The lungs were apparently normal, the heart regular and the pulse rate 100 beats per minute. The arterial blood pressure ranged from 125 to 195 systolic and from 80 to 100 diastolic. There were definite periods of apnea. Except for the abdominals, the reflexes were completely absent. There was a marked cyanosis. There was no evidence of facial paralysis and no rigidity of the neck.

Spinal puncture yielded clear fluid under slightly increased pressure. It contained about 100 crenated red cells, but no white cells. The Wassermann, Nonne, and Ross-Jones tests were negative. The leukocyte count at that time was 32,000, the red blood cell count 5,350,000, hemoglobin 90%. The urine showed traces of albumin and glucose; there was neither acetone nor diacetic acid; the specific gravity of the urine was 1020. The patient's temperature gradually rose to 101.2°, his pulse increased to 120 beats per minute. His respiration continued to be Cheyne-Stokes in character and periods of apnea occurred every 50 to 70 seconds. Just before death, the patient's respiration became more labored and decreased to 6 per minute. He died 20 hours after the onset of the illness.

Necropsy revealed bilateral hemorrhagic bronchopneumonia; healed endocarditis of the mitral valve; moderate arteriosclerosis of the aorta and coronaries; and slight myocardial fibrosis. There was also a healed apical tuberculosis. The surface of the brain was bluish-purple; the gyri were markedly flattened, the sulci obscured. The subarachnoid vessels were hyperemic. The hyperemia was especially pronounced in the region of the cerebellum and pons. The internal capsule seemed much darker than normal. The basal ganglia also seemed darker than normal and appeared somewhat granular. Markedly dilated vessels and minute petechial hemorrhages were seen throughout the entire white substance of the brain.

Microscopic examination of the brain revealed a variety of changes. The bloodvessels throughout, and particularly the capillaries, were packed with red cells, the outlines of which were clearly recognizable. In many sections there was a distinct extravasation of red blood corpuscles into the perivascular spaces. Some of the sections also revealed foci of hemorrhage without any recognizable bloodvessels in these particular regions. Some of the bloodvessels showed small rings of a hyalin-like material lining their inner walls. Other sections showed many neutrophils at the periphery of the lumen of the vessels and also infiltrating their walls. In many instances, a distinct perivascular infiltration of neutrophils could be made out. These changes were seen throughout the gray and the white substance, but were more pronounced in the latter. Sections taken through the basal ganglia also revealed a marked hyperemia and extravasation of red blood cells. In addition to these changes, however, many ganglion cells without any recognizable nuclei were seen. In some instances, the cytoplasm of these was granular; in others it seemed to be arranged in clumps. Other ganglion cells were completely transformed into hyalin-like globules. In some instances, but especially noticeable within the pons, cerebellum and locus caeruleus, a few bloodvessels were surrounded by lymphocytes. Here and there a few clumps of blood pigment granules were also noted. Other sections showed an apparent atrophy of rows of ganglion cells with pyknotic nuclei. Occasionally, there were seen dark-bluish stained, well-outlined bodies (corpora amylacea). There was also a slight increase in glia cells and fibers in the region of the locus caeruleus, replacing ganglion cells. The Davenport stain indicated a diminution of nerve fibers in these sections. Degeneration of the myelin sheaths was also noted. Cocci were very rarely present within the walls of the vessels. In only one field were they found outside the vessels invading the surrounding brain tissue. The cocci were arranged in groups of two and were Gram-positive.

Summary of Case 5. The short duration of the disease is again impressive. It is of interest that there was but slight clinical evidence of the bronchopneumonia, although it was of longer duration than the acute encephalitis, which we believe was the cause of death. The clinical picture was apparently completely dominated by the encephalitis. The coincidental presence of the acute and old encephalitis will be discussed later.

Discussion. These 5 cases of encephalitis were all fulminating. In one instance, death was sudden; in the others, it occurred unexpectedly within $4\frac{1}{2}$ hours, 12 hours, 20 hours, and 48 hours, after the onset of the illness. The severity of the encephalitis in all of these cases makes us believe that in spite of pneumonia in 4 cases and of whooping cough in the fifth, the cause of death was encephalitis.

One of the outstanding symptoms, if not the chief symptom, in our patients, was the respiratory difficulty, which was variously described as dyspnea, stertorous breathing, and Cheyne-Stokes respiration. In one, the respiratory difficulty was so marked that the presence of a foreign body in the trachea was considered. The respiratory difficulty was always accompanied by cyanosis.

The cerebrospinal fluid removed from the 3 patients who lived long enough to allow a spinal puncture to be done, was clear, colorless, and under increased pressure. One specimen of cerebrospinal fluid contained no cells, another 5 white blood cells and still another contained 11, 2 being within normal limits and 1 only slightly increased. The fluid in 2 cases contained many red blood cells. The question arises as to whether or not the presence of the red blood cells is of any significance. If it were possible to exclude the factor of trauma, the presence of the red blood cells would be important and would speak for hemorrhagic encephalitis. However, it is possible that the red blood cells were due to trauma caused by the spinal puncture, for no matter how clear the cerebrospinal fluid, it is still possible that there was some trauma to the venous plexus of the cord. One must therefore attach no diagnostic importance to the presence of red blood cells in the fluid, although, as stated, they may be significant. There was no increase in globulin in the cerebrospinal fluid in any of the three specimens. In one, the cerebrospinal fluid sugar was increased, judging by the fact that the method used for the determination was the one described by Somogyi,¹ by which non-meningitic and encephalitic fluid usually contains 80 mg. sugar or less per 100 cc. (Cohn, Levinson and McCarthy).² Yet the increase was only slight (5 mg.+) and therefore no diagnostic conclusions could be drawn from the cerebrospinal fluid sugar in this case.

The results of the cerebrospinal fluid examination of these 3 patients corroborates the previous statement by one of us (Levinson)³ that there is no uniformity in the cerebrospinal fluid changes

in encephalitis. It is thus possible that in instances of encephalitis there may be marked cerebrospinal fluid changes, moderate changes or no changes whatsoever.

We believe that the cerebrospinal fluid changes depend upon the meningeal involvement; the greater the meningeal involvement, the more pronounced the cerebrospinal fluid changes.

Of great interest to us was Case 5, in which the encephalitis which caused the patient's death was apparently superimposed on an old encephalitis. The increase in glia cells and capillaries, the alteration of the nerve fibers and myelin sheaths, the presence of blood pigment and lymphocytes, were characteristic (McAlpine).⁴

It may be of interest to note that after the histologic examination in Case 5 was completed, and after the changes characteristic of an old encephalitis were found, the relatives were asked for further information. It was then learned that in 1917 the patient had suffered an attack of influenza. No definite information as to a possible encephalitis at that time could be obtained, but it had been noted that since that time his facial expression had gradually changed and had become mask-like. His movements had gradually become slower.

The simultaneous occurrence of recent and old encephalitis has been observed by us in another instance. It is a matter of speculation whether the old encephalitis had caused a local lack of resistance favoring the recent encephalitis—either mechanically or immunologically—or whether the presence of the old and recent encephalitis in the same brain was a coincidental occurrence.

The presence of Gram-positive diplococci in the brain in this case is noteworthy. Economo⁵ and v. Wiesner⁶ believed that a diplo-streptococcus is the causative agent of lethargic encephalitis. There is, however, no evidence that the bacteria had caused the encephalitis in our case, particularly because they were found principally in the bloodvessels. Zinsser⁷ says that "logic forces one at the present time to reject the bacterial causation of this disease (epidemic encephalitis)."

It is interesting that bronchopneumonia was found at autopsy in the 4 instances in which the lungs could be examined. Clinically, evidence of bronchopneumonia was present in only 1 instance. The recognition of bronchopneumonia may have been more difficult, first, because the area involved was small, and second, because the symptoms were masked by the encephalitis. In Case 5, the bronchopneumonia was at least 3 or 4 days old and yet the patient, who was a physician, did not complain of being sick. It is possible that the respiratory tract was the portal of entry for the causative agent of the encephalitis.

Histologically, these 5 cases may be classified into two groups. The outstanding features in the first 3 brains were the extravasation of red blood corpuscles in addition to the infiltration of lympho-

cytes and a few neutrophils. It is known that the extravasation of red blood corpuscles may occur in cases of general intoxication, constitutional disturbances, etc. (Hassin)⁸ However, in addition to the red blood corpuscles, other cellular elements were found in the perivascular spaces in sufficient numbers to warrant the diagnosis of encephalitis. The extravasation of red blood corpuscles is one of the earliest histologic findings in these cases. This is borne out by the fact that, as far as can be determined from the clinical history, the duration of the disease in our patients was extremely short. In the last 2 brains, a larger number of neutrophils was present. However, red blood cells and lymphocytes were also found free in the tissue in these 2 cases. In his study of lethargic encephalitis, Economo⁵ described minute accumulations of neutrophils, without destruction of the brain tissue in addition to red cells and lymphocytes, in only 1 case, while neutrophils were absent in the other case.

The rapid occurrence of death of the 5 patients is striking. If an autopsy had not been performed in the first case, it probably would have gone on record as death "due to the ingestion of a foreign body." In other words, it must be realized that fulminating encephalitis may be the cause of sudden, unexpected death. It may be mentioned in this connection that Kolisko,⁹ in his comprehensive monograph on "Sudden Death from Natural Causes," does not mention encephalitis as a cause of sudden death.

In view of the enlarged thymus in the first child and of the marked hyperplasia of the lymphadenoid structures in the first 3 patients, it should be decided whether or not these children should be classified as having status thymolymphaticus and whether or not the suddenness of the onset of the disease and death can be linked with status thymolymphaticus. There is still much discussion as to whether or not this status can be linked with a general lowered resistance of the tissue. Ever since the report of the British Commission on this question (Young and Turnbull)¹⁰, the assumption of status thymolymphaticus has fallen into discredit. And yet, in doing routine autopsy examinations, one comes across a rare instance of the sudden death of an individual who had a large thymus and generalized hyperplasia of the lymphadenoid structures. Death in such a case may have followed an insignificant trauma. If such a case reveals at autopsy the absence of inflammatory lesions which *per se* might have been responsible for the hyperplasia of the lymph nodes, we believe that the assumption of a status thymolymphaticus is still justified, at least because it provides a morphologic explanation for the sudden and unexpected death. In the first 2 cases of encephalitis, the duration of the disease was so short that we cannot believe that the acute inflammation had caused the general lymphoid hyperplasia. In our opinion, the rapidity of the course of the disease and death of these children may be explained

by the assumption of a general lowered resistance which had its morphologic equivalent in the enlargement of the lymphadenoid structures throughout the body. In the third patient with encephalitis, however, the inflammatory changes were marked and this alone may explain the hyperplasia of the lymphadenoid tissue. In other words, the suddenness of the deaths of some of the patients reported here cannot, in our opinion, be explained on the basis of a status thymolympathicus, but must be regarded solely as the result of the fulminating encephalitis.

Various types of encephalitis have been described in the literature. Some authors stress the epidemic occurrence (epidemic encephalitis), some emphasize the particular symptoms (lethargic encephalitis), while others point to characteristic gross or histologic findings (hemorrhagic encephalitis, etc.). Neither clinically nor morphologically can we be absolutely certain as to which group of encephalitis our cases belong. The redness of the brain and the predominance of the hemorrhagic exudate which were found in every instance justify the anatomic term "acute hemorrhagic encephalitis." It may be stressed that this disease had occurred sporadically and there was not a single instance where it was transmitted to anyone who came in contact with the patient. As stated before, the outstanding clinical feature common to all 5 of our cases of encephalitis was the rapidity of its course and of the death of the patients. This was so striking to us that we believe that the term "pernicious" or "fulminating" encephalitis is justified to describe fully the most outstanding clinical picture.

The diagnosis of encephalitis is always difficult, since the disease must be differentiated from other acute infections of the central nervous system, particularly from tuberculous meningitis, brain abscess and brain tumor, and from what is commonly called meningism. However, fulminating encephalitis, as we have here described it, presents the further difficulty in that it must be differentiated from conditions which lead to sudden death and which do not involve the central nervous system, such as foreign bodies in the lungs, and circulatory collapse.

Summary and Conclusions. Fulminating hemorrhagic encephalitis is characterized by sudden onset, great respiratory difficulty, coma, and rapid death. The course of the disease is very short and death may sometimes be sudden. The cerebrospinal fluid may be hemorrhagic, but is usually clear. It may have an increase in cells, or may show no changes. The greater the meningeal involvement, the more pronounced the cerebrospinal fluid changes. Histologically, the brain reveals a predominance of a hemorrhagic exudate in addition to perivascularly arranged lymphocytes and neutrophils. In one instance, fulminating hemorrhagic encephalitis was found superimposed on an old encephalitis. In children, a generalized enlargement of the lymphadenoid apparatus is usually present. The

sudden death due to fulminating hemorrhagic encephlitis may be regarded as an example of "sudden death from natural causes," in Kolisko's definition of the term.

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CARBOHYDRATE METABOLISM IN HUMAN HYPOTHYROIDISM INDUCED BY TOTAL THYROIDECTOMY.

III. A CASE OF DIABETES MELLITUS TREATED BY TOTAL ABLATION OF THE NORMAL THYROID GLAND.*

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For several years it has been recognized that diabetes mellitus is aggravated by thyrotoxicosis and benefited by myxedema.

Many investigators, including Fitz,¹ Wilder,² John,³ Joslin and Lahey,⁴ and Andersen⁵ have observed that the diabetic condition

* The first and second papers of this series appeared in this Journal, **188**, 790 and 796, 1934.

of patients with diabetes and thyrotoxicosis was alleviated markedly after subtotal thyroidectomy. Similarly, others have reported amelioration of diabetes associated with thyrotoxicosis, following iodine treatment^{6,7} and following Roentgen⁸ therapy.

Rohdenburg,⁹ and Weinstein¹⁰ observed patients in whom all clinical evidences of diabetes disappeared as myxedema spontaneously developed. Wilder² also has reported a case in which the carbohydrate tolerance increased markedly when spontaneous myxedema developed. Weinstein¹⁰ found that the evidences of diabetes reappeared in his patient when the basal metabolism was brought again to normal by thyroid. Other investigators also have found that the diabetic condition became aggravated when patients with diabetes and myxedema were given thyroid^{2,5,10-14} and that when thyroid medication was discontinued in these patients, diabetes again became less severe.^{2,11,12,13}

These striking clinical indications that a lowering of thyroid activity benefits diabetes led us in November, 1933, to consider treating a patient with uncontrollable diabetes and incipient tuberculosis by the induction of hypothyroidism through total ablation of the thyroid gland. The patient had mitral stenosis and sufficiency but had never experienced any symptoms nor shown any signs of congestive failure. This patient had no evidences of thyrotoxicosis and the basal metabolic rate averaged +7%. The usual methods of treatment had failed to control her diabetes. It was hoped that by producing hypothyroidism the diabetes might be alleviated and the progress of the tuberculosis be retarded indirectly. In previous studies of the control of hypothyroidism after total thyroidectomy in patients with chronic heart disease, it had been found that a basal metabolic rate of approximately -25% to -30% could be maintained without discomfort to the patient.^{15,16} Total ablation of the thyroid gland according to the technique of Berlin¹⁷ was therefore performed in this patient after a thorough explanation of the situation to her.

Case Report. On May 16, 1931, Mildred D. (B. I. H. Case 10811) a 22-year-old, American-born, Jewish housewife, entered the Beth Israel Hospital complaining of marked loss of weight for 4 months, and polydipsia, polyuria, and polyphagia for 1 month. The family history was negative; the past history was essentially negative except for the presence of a cardiac murmur since the age of 12, at which time she had had a severe attack of chorea. The urine at the time of admission showed complete reduction for sugar and 4+ acetone. The fasting blood sugar was 192 mg. per 100 cc.* The body height was 62 inches and the weight 110 pounds. The B. M. R. was -13%. Hematological studies revealed normal findings. The patient remained in the hospital 13 days during which time the diabetes was controlled by a diet consisting of 110 gm. of carbohydrate, 50 gm. of protein, and

* Blood sugar measurements were made by the method of Folin.¹⁸ Plasma cholesterol measurements by the method of Bloor¹⁹ and basal metabolic rates using a Collins-Benedict-Roth spirometer and calculating according to the normal standards of Aub and Dubois.²⁰

70 gm. of fat (1270 calories), and 10 units of insulin daily. She was discharged to the Diabetic Clinic of the Ont Patient Department on this same régime. Because of loss of weight during the next 2 months, her diet was gradually increased to 180 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat (2300 calories), and the insulin to 20 units daily.

In February, 1932, the patient returned to the Clinic after an absence of 6 months, during which time she had had a therapeutic abortion and had not adhered to her dietary and insulin routine. At this time her diabetes was so severe that 66 units of insulin daily, divided in three doses, were required.

In June, 1932, she was admitted into the wards with signs of subacute appendicitis. An appendectomy was performed. The operation and convalescence were uneventful. She remained in the hospital 55 days, during which time it was extremely difficult to control the diabetes adequately. The fasting blood sugar values were repeatedly approximately 350 mg. per 100 cc., the insulin dosage from 40 to 80 units daily. During the next 15 months the patient returned to the Diabetic Clinic every 1 to 2 weeks. Many dietary and insulin adjustments were attempted. She was finally regulated on a diet of carbohydrate 130 gm., protein 80 gm., fat 120 gm., totalling 1900 calories, and 66 units of insulin divided in three doses daily. On this régime she did fairly well for about a year, although sugar was still repeatedly found in the 24-hour urine, and changes from insulin reactions at one time of the day, to gross glycosuria at other times were frequent.

On October 23, 1933, because of the steadily increasing severity of her diabetes, and the development of lung lesions she was readmitted to the hospital. Her weight at this time was 112 pounds. She complained of general weakness. Examination of the lungs revealed dullness, increased transmission of breath sounds, and occasional crepitant râles over the right apex. Stereoroentgenographic examination of the lungs revealed an area of increased density at the right apex, the central portion of which contained an ovoid area of diminished density, suggesting early cavitation. There was no cough, hemoptysis, or night sweats, the temperature was normal, but the pulse rate ranged between 80 and 100. A diagnosis of pulmonary tuberculosis was made. The patient also had mitral stenosis but had at no time experienced signs or symptoms of heart failure, nor had her activities been limited by the cardiac condition.

During the 2 weeks between October 23 and November 6, 1933, in the hospital, she was maintained at complete bed rest. On a diet of 140 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat (2140 calories), she required as much as 105 units of insulin daily divided in four doses. In spite of this, her diabetes remained uncontrolled. The blood sugars varied from very high to very low figures during the same day in spite of adjustments in insulin and diet.

The treatment of this patient with severe diabetes and tuberculosis of the lungs was an extremely difficult problem. She obviously required meticulous supervision of her diabetes and bed rest for her tuberculosis. Financial and social circumstances prevented her from receiving adequate treatment at home. The diabetic condition was intractable under the optimum conditions in the hospital and so it was deemed unwise to submit her to the less closely supervised régime of the average sanatorium.

On November 6, 1933, total ablation of the thyroid gland was performed, in the hope that hypothyroidism might alleviate the diabetes and thereby also have a favorable effect upon the tuberculosis. The postoperative course was uneventful. On pathologic examination the thyroid gland was found to be normal. The patient remained in the hospital under close observation for 5 months.

The average basal metabolic rate before operation was +7%; the body

weight 111 pounds (Chart I). During the 5 postoperative months the patient was confined to bed, because of the tuberculosis, and given the same diet as that just prior to operation, namely: 140 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat (2140 calories). Following operation, the B. M. R. decreased gradually, and at the same time the insulin requirements also decreased (Chart I). Failure to decrease the amount of insulin occasionally resulted in mild insulin reactions. The B. M. R. 45 days after operation had decreased to -30% and the insulin requirement to 35 units daily. The body weight had increased to 118 pounds. From the 50th to the 82d postoperative days the basal metabolic rate ranged between -30% to -35% and the insulin requirements varied from 35 to 50 units daily. The plasma cholesterol concentration was high (Table 1). By the 82d postoperative day her body weight had increased to 127 pounds. Beginning approximately 2 months after operation, the patient experienced some weakness and drowsiness. These symptoms became gradually more severe so that beginning on the 82d postoperative day she was given small amounts of desiccated thyroid (gr. $\frac{1}{4}$ daily, Armour). During the 10 days on this medi-

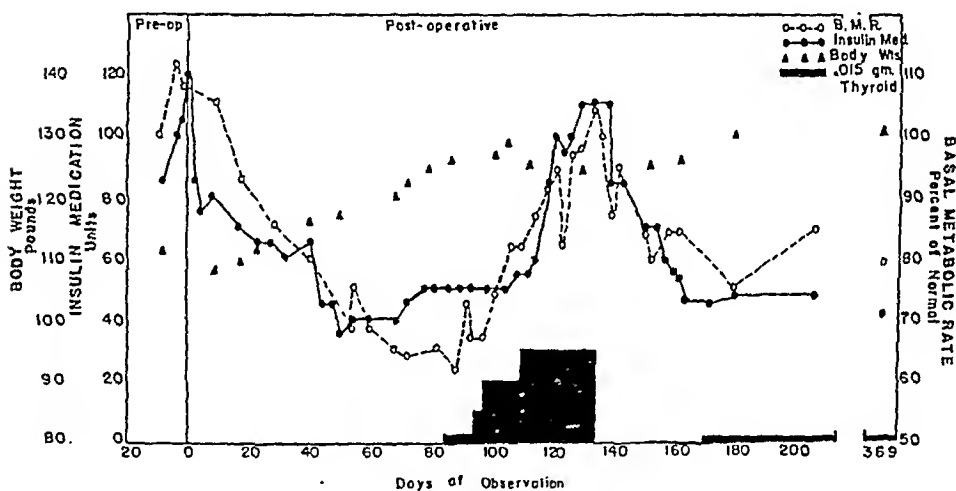


CHART I.—Effect of total thyroidectomy on insulin requirement.

cation the B. M. R. increased from its lowest value of -38% to approximately -30% ; the insulin dosage remained 50 units daily (Chart I). The symptoms of myxedema were relieved.

In order to determine whether the postoperative decrease in insulin requirement of this patient was due to the development of hypothyroidism, or to some other factor, sufficient thyroid was administered to raise the metabolism to the pre-operative level. The thyroid medication was increased gradually, and 135 days after operation the B. M. R. had increased to $+5\%$ (Chart I), and the serum cholesterol had decreased to normal (Table 1). The patient now presented the same intractable diabetes as before operation; 110 units of insulin daily again were required (Chart I).

Thyroid medication was omitted and the B. M. R. and insulin requirements again decreased (Chart I).

On April 15, 1934, 5 months after operation, she was discharged to the Diabetic Clinic of the Out Patient Department with practically the same diet (carbohydrate 140 gm., protein 80 gm., fat 120 gm., totalling 1960 calories) as that employed throughout the study, and 46 units of insulin daily divided in three doses. Her B. M. R. at this time was -20% . She was allowed up

and about and to do light work. On May 3, with the B. M. R. at -24% , and 46 units of insulin daily divided in two doses some weakness was again experienced so that thyroid grains $\frac{1}{16}$ daily were prescribed.

TABLE 1.—EFFECT OF TOTAL THYROIDECTOMY ON THE BASAL METABOLISM, PLASMA CHOLESTEROL AND INSULIN REQUIREMENT.

	Date	Basal metabolic rate, % deviation from normal.	Plasma cholesterol, mg. per 100 cc.	Insulin units.	Daily thyroid medication, grn.
Oct.	25, 1933	+ 2	...	95	
Nov.	2, 1933	+12	..	100	
Nov.	5, 1933	+ 8	..	105	
Nov.	6, 1933	Total ablation of normal thyroid gland.			
Dec.	1, 1933	-14	...	65	
Dec.	16, 1933	-20	...	55	
Dec.	26, 1933	-32	520	45	
Jan.	13, 1934	-35	694	40	
Jan.	31, 1934	-34	...	50	.015
Feb.	15, 1934	-26	510	50*	.120
Feb.	24, 1934	-13	208	60*	.180
March	10, 1934	- 3	189	100	.300
March	18, 1934	+ 5	166	110*	.300
March	24, 1934	-13	245	85*	
May	3, 1934	-24	...	48	
May	29, 1934	-15	463	48	.007
Aug.	30, 1934	-17	284	48	.007
Nov.	10, 1934	-21	390	42	.007

* Indicates that the urine showed sugar during the entire 24 hours and that more insulin was required.

From May 1934 to November, 1934 the same diet prescribed on discharge from the hospital was given. Between 42 and 48 units of insulin daily proved sufficient to control the diabetic condition. Because of financial difficulties, the patient did not follow the dietary régime on a few occasions and glycosuria occurred. On one of these occasions she was admitted to the wards for proper regulation and was discharged in 10 days on the same diet and the same amount of insulin on which she was stabilized before, namely, 44 units daily divided in two doses. With the exception of these few occasions, the urine has been sugar-free most of the day. The body weight has been approximately 130 pounds. Her B. M. R. has remained approximately -20% . Except for a short period when she complained of cramps in the calves of the legs and occasionally in the feet, she has been free from symptoms of myxedema, receiving thyroid grains $\frac{1}{16}$ daily.

It is interesting to note that for several months following thyroidectomy, she had difficulty in recognizing insulin reactions,²¹ the only symptom being that of precordial or epigastric weakness. Beginning October, 1934, the characteristic symptoms of sweating and inward trembling sensation have returned.

The pulmonary process in this patient has become arrested. On March 23, five months after operation, Dr. Mark Joress of the Pulmonary Clinic made the following observation: "A summary of symptomatology, physical examination and radiographic findings warrants, I believe, the opinion that the tuberculosis is showing a constant regression." On examination 6, 9 and 12 months after operation, no clinical or Roentgen ray signs of

activity in the lungs could be found. On November 1, the Roentgen ray report states "re-examination of the chest shows the areas of increased density in the upper portion of the right lung field still present, but there are no progressive changes in the lungs."

Since this paper has been in press the patient has maintained her clinical improvement. On May 9, 1935, she was found to require 40 units of insulin daily. The midday blood-sugar concentration was 124% mg., the serum cholesterol was 328% mg., and the urine specimens during the entire 24 hours were sugar-free.

Discussion. The therapeutic results obtained by total thyroidectomy in this patient have been gratifying up to this time, 1 year after operation. On an adequate diet her diabetes has been controlled with 42 to 46 units of insulin daily, divided in two doses, while prior to the operation her diabetes could not be controlled adequately even with 85 to 105 units daily. The tuberculosis has been arrested by 5 months of bed rest following operation and probably also in some measure through the alleviation of her diabetic condition. At the level of hypothyroidism (B. M. R. of approximately -20%) maintained in this patient by the administration of small doses of thyroid (Armour's gr. $\frac{1}{16}$ daily), she suffers no appreciable discomforts. She now leads a happy and useful life, taking care of her home for her family. She looks more healthful than before operation, partly because of the gain in weight. Her general appearance is in no manner that of a patient with myxedema.

Observations of the effect of total thyroidectomy on the carbohydrate metabolism of experimental diabetes in animals have been discussed in the second paper of this series.²² O'Day, in 1915,^{23,24} removed the "greater portion" of the thyroid gland in 2 young patients with diabetes and no evidence of thyroid disease. During the first few postoperative months these subjects showed a marked increase in tolerance,²³ but subsequently both patients died in diabetic coma.²⁴ In view of the fact that maximal subtotal thyroidectomy may cause only temporary hypothyroidism,²⁵ it seems possible that permanent hypothyroidism was not effected in O'Day's cases with diabetes. Crile,^{26,27} also in 1915, performed section of the cervical sympathetic, left suprarenalectomy and partial thyroidectomy in a patient with diabetes. While satisfied with the results obtained in this patient, Crile was unwilling to ascribe the improvement entirely to the operation because the Allen treatment was employed at the same time.²⁷

A few weeks after our patient was operated upon, Wilder, Foster and Pemberton²⁸ reported a case of severe uncomplicated diabetes and no thyroid disease in which radical thyroidectomy was done on May 30, 1933. The development of hypothyroidism was accompanied by a marked increase in sugar tolerance which paralleled roughly the decrease in the B. M. R. One year after operation, the patient required 15 units of insulin daily at a level of hypo-

thyroidism compatible with freedom from discomforts of myxedema, whereas prior to operation he had required approximately 30 units daily.^{2,5,29}

The improvement of the diabetes in Wilder's patient and in our patient after the development of induced hypothyroidism is in accord with the improvement in diabetes which has been observed to attend the development of spontaneous myxedema.^{2,9,10} That the diabetes in our patient again returned to its pre-operative severity when the B. M. R. was raised to its pre-operative level by thyroid medication (Chart I), is in accord with the finding that diabetes is rendered more severe when the basal metabolism is increased by thyroid medication^{2,5,10-14} or by thyroid disease.¹⁻⁵ The improvement in the diabetes of our patient was not related to subsidence of the tuberculosis, for raising the metabolic rate by thyroid to the pre-operative level again reproduced the severe diabetic state witnessed before operation.

In order to remain free from the discomforts of myxedema our patient requires grains $\frac{1}{16}$ of thyroid (Armour's) daily. On this thyroid dosage a hypothyroid state is maintained with a level of basal metabolism of approximately -20%. This principle of maintaining a hypothyroid patient at a level of metabolism just sufficiently high to avoid the severe symptoms of myxedema should be applicable likewise in those patients with spontaneous myxedema and diabetes whose diabetes becomes severe when the basal metabolism is brought to normal by thyroid.

The elevated blood cholesterol values found at intervals after total thyroidectomy (Table 1) in this patient were related, apparently, to the degree of hypothyroidism rather than to the diabetic state. Very high cholesterol values were obtained during the third post-operative month when the B. M. R. was very low and the patient was experiencing distressing symptoms of myxedema such as weakness and drowsiness. This is in accord with previous observations following total thyroidectomy in patients with chronic heart disease.³⁰ When the B. M. R. was returned to normal by thyroid medication, the concentration of serum cholesterol became normal, subsequently increasing again as the B. M. R. decreased following reduction in thyroid medication (Table 1).

The mechanism through which diabetes is benefited by hypothyroidism is not entirely understood. In the first communication of this series³¹ it was pointed out that in non-diabetic patients, hypothyroidism induced by total thyroidectomy had but little effect on the glucose tolerance curve and the concentration of the sugar of the serum after a fast. On the other hand the carbohydrate tolerance of a patient with mild diabetes, in whom total ablation of the normal thyroid gland was performed for the relief of angina pectoris, increased considerably after hypothyroidism developed.³¹ The glucose tolerance curve also became considerably more like

normal when hypothyroidism developed after total thyroidectomy in a patient who before operation had mild hyperthyroidism and an abnormal glucose tolerance curve.³¹ In the second communication of this series,²² it was shown that the effect of the subcutaneous injection of 20 units of insulin on the blood sugar of non-diabetic patients was the same before and after the development of hypothyroidism; in 6 patients 20 units of insulin caused an average maximum decrease of 34% in the blood sugar before operation and the same average decrease after hypothyroidism developed. Fitz¹ has suggested that a lowering of the B. M. R. affords improvement in patients with diabetes. Wilder^{28,29} accounts for the improvement in diabetes, which accompanies the lowered B. M. R. in hypothyroidism, by an increased sensitivity to insulin. Joslin,³² before the insulin era, found that the metabolism in diabetes was greatly influenced by high and low diets.

Although maximal subtotal removal of the normal thyroid gland in man occasionally may produce permanent hypothyroidism,^{25,29} evidence has been presented^{25,33} that total removal of the normal thyroid gland must be performed in order to insure permanent hypothyroidism in every instance. In 2 patients with heart disease in whom maximal subtotal removal of the normal thyroid gland was performed at the Beth Israel Hospital²⁵ hypothyroidism did not persist. Other investigators have reported similar experiences.^{34,35}

Means and Herman³⁶ have described the rate of decrease in B. M. R. following the abrupt cessation of thyroid medication in patients with myxedema. From the B. M. R. studies in our patient it is evident that the rate of decrease of metabolism is approximately the same following total ablation of the normal thyroid gland and cessation of thyroid medication which has restored the B. M. R. to normal (Chart I). The rate of decay of thyroid activity, both after total thyroidectomy and after thyroid medication in this patient accords with the findings of Means and Herman.³⁶

The severity of the diabetes in our patient, together with the complication of tuberculosis, appeared to justify the attempt to benefit her by inducing hypothyroidism through total ablation of the normal thyroid gland. This procedure obviously is not applicable to the treatment of diabetes mellitus unless the case is of marked severity and uncontrollable by the usual therapeutic measures. Wilder and his associates²⁹ concluded from their study of the effect of hypothyroidism induced by radical thyroidectomy in a patient with diabetes that "the remedial result was not sufficient to justify recommending the procedure as a treatment." It should be noted that their patient on an adequate diet required only 30 units of insulin daily before hypothyroidism was induced. From the results in our case of severe diabetes we feel that unusual patients with diabetes of similar severity and unstable character may benefit from total thyroidectomy.

Summary. 1. A patient with severe uncontrollable diabetes mellitus complicated by tuberculosis of the lungs was treated by total ablation of the thyroid gland. Before operation, the B. M. R. was +7% and the patient showed no evidences of hyperthyroidism. The extirpated thyroid tissue was found normal on gross and microscopic examination.

2. The diabetic condition which could not be adequately controlled prior to operation under optimal conditions with diet and an average insulin dosage of 95 units daily was readily controlled by diet and 44 units of insulin daily after hypothyroidism developed.

3. A level of hypothyroidism at which the patient remained free from any unpleasant symptoms of myxedema was maintained by very small doses of thyroid.

4. It is suggested that the treatment of hypothyroidism with very small doses of thyroid as applied in this patient may be useful also in some patients with diabetes and spontaneous myxedema.

5. As evidence that the reduction in insulin requirements in our patient was due to the hypothyroid state, it was found that administration of thyroid sufficient to restore the pre-operative metabolic level resulted in relapse of the patient's diabetic condition to the pre-operative status.

6. Total thyroidectomy is not advised in the treatment of diabetes mellitus except in the rare case with very severe diabetes which cannot be controlled adequately by the application of all known therapeutic measures.

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- (Titles have been omitted for sake of brevity.)

THE VARIABLE AUSCULTATORY SIGNS OF PULMONARY CAVITIES.*

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Most of the pulmonary cavities, irrespective of whether they are tuberculous, bronchiectatic, acute suppurative, or neoplastic in origin, do not reveal their presence by cavernous breath sounds. In 350 cases of pulmonary cavities which I have studied at the Sea View, Cumberland, and New York Post-Graduate Hospitals, I found that 246 lack most if not all of the classic auscultatory signs of cavitation. However, I want to stress from the start that these findings in no way disparage the diagnostic importance of the stethoscope, but merely point to the necessity of revising the hitherto accepted physical signs of cavities and their probable mechanism. Whereas pectoriloquy and amphoric breathing may be heard over an old fibroid lesion which is of little clinical significance, very scanty signs may be elicited over an active pulmonary cavity which requires immediate therapeutic attention. Of the 246 cases which lacked cavernous breathing, 36 revealed no inkling of the presence of any pulmonary lesion, but the rest of the cases manifested certain adventitious signs which when systematized properly proved helpful in the diagnosis of cavities.

The 350 cases of pulmonary cavities which I have studied, may be divided into four groups as far as auscultatory signs are concerned: *a*, Cavities which manifest themselves through the classic cavernous signs; *b*, cavities over which no suspicious signs of any pulmonary

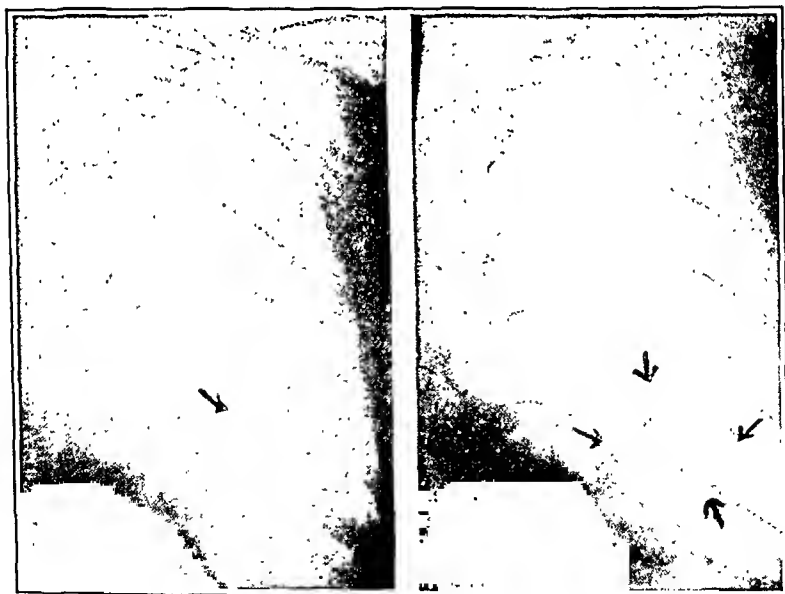
* Presented at the Research Society and Journal Club of the New York Post-Graduate Medical School, November 13, 1934.



A

B

FIG. 1.—*A*, Two adjacent small cavities in outer zone of left pulmonic field. The only adventitious sign elicited over this area was coarse râles after cough. *B*, Cavity in midzone of right pulmonic field (note fluid level). Altered breath sounds and moist inspiratory râles were limited to this area anteriorly, but no adventitious signs were elicited posteriorly.



A

B

FIG. 2.—*A*, Caseous lesion in left lower lobe, but no definite cavity is outlined on the roentgenogram. Auscultation revealed modified breath sounds and crepitant râles on ordinary inspiration, limited to same area anteriorly and posteriorly. *B*, A roentgenogram of the same case after induction of left artificial pneumothorax. Note the well-outlined cavity and its thick capsule.

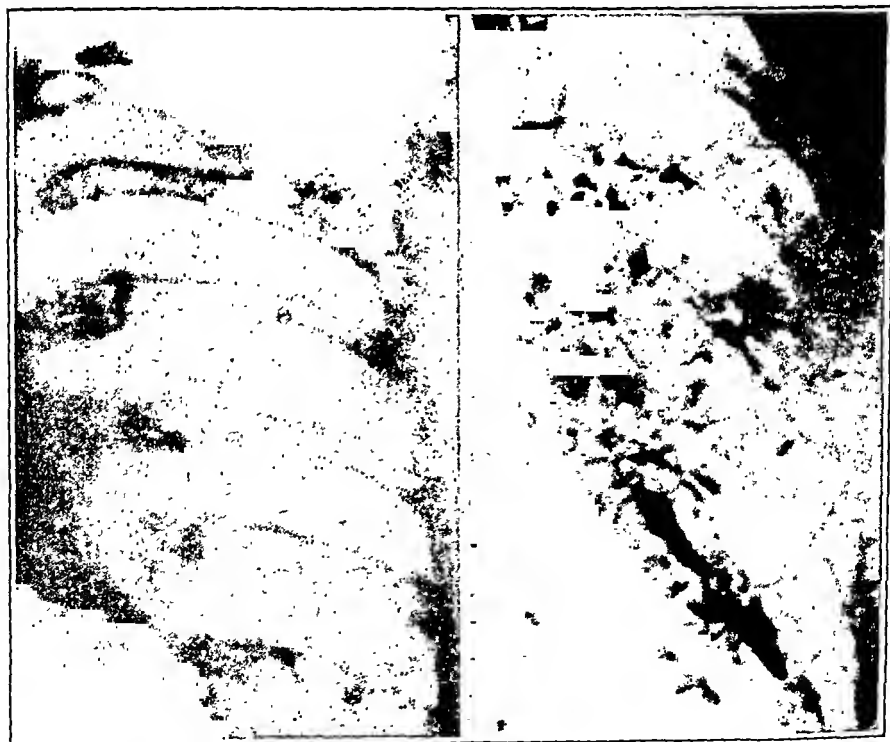


A

B

C

FIG. 3.—*A*, A large cavity in right upper lobe with all the classic cavernous signs. *B*, Same case after injection of 300 cc. of air into pleural cavity; only altered breath sounds and coarse inspiratory râles are now heard over subclavicular fossa. *C*, A roentgenogram a few weeks later shows cavity reduced in size; cough and deep breathing elicit only a few râles over area of cavitation.



A

B

FIG. 4.—*A*, No definite lesion is visible, though cavernous breathing was heard over left lower lobe. *B*, Same case after bronchography, revealing 2 bronchiectatic cavities communicating by a small narrow canal.

lesion can be elicited; these I named absolutely mute; *c*, relatively silent, *i. e.*, such cavities which do not exhibit any of the classic signs but over which other adventitious sounds are heard, such as altered breath sounds, modified whispered voice, inspiratory râles over a limited area, etc.; *d*, intermediate, *i. e.*, such cavities which at times are absolutely silent and at other times reveal themselves by certain adventitious stethoscopic signs, thus belonging alternately to Groups *b* and *c*.

The following table indicates the order of frequency of the four groups of cavities:

TABLE 1.—FREQUENCY OF 4 TYPES OF CAVITIES.

	No. of cases.	Frequency, %.
Total number	350	
Relatively silent cavities	177	50.6
Cavities with cavernous breathing	104	29.7
Intermediate cavities	36	10.3
Absolutely mute cavities	33	9.4

It is evident from these figures that the relatively silent cavities are by far the most prevalent. Their "silence" applies only to cavernous sounds, otherwise they invariably manifest themselves through certain congeries of stethoscopic signs. The figures also clearly indicate that cavernous breathing, as a diagnostic criterion of a cavity, takes only a second place, for it was present in only about 30% of all cavities. On the other hand, it is of clinical significance to note that a small number of pulmonary cavities cannot in any way be detected by physical signs (33 cases out of a group of 350 cases). If we also add the intermediate cavities to these so-called absolutely mute ones, the total would be increased to 69 cases, which would mean that at most about 20% of all pulmonary cavities could not be detected by physical signs alone. However, in about 80% of all pulmonary cavities the stethoscope was sufficient to diagnose or at least to suggest the presence of a cavity.

The question arises, what are the factors which modify the physical signs of a cavity, and what bearing have they on the clinical course and possible therapeutic procedure to be followed? Without going into a detailed discussion of breath sounds in general, it might be stated that two views prevail: 1, that they are produced in the larynx; 2, that they originate in the chest. Bushnell¹ seems to have proven experimentally that the breath sounds are produced in the larynx, but are modified by conduction and sympathetic vibrations of the lung tissue and thoracic cavity. Chanveau,² on the other hand, seems clearly to have established the fact that experimental obliteration of the glottic sound does not annul the inspiratory sound heard by auscultation over the lung. Hence, he believes that it originates in the chest itself. Neither of these views alone can explain the production of cavernous sounds. It is possible

that a laryngeal element is present in all breath sounds, but the inrush of air into the cavity and the sympathetic vibrations set up in its wall are principally instrumental in imparting the blowing cavernous tinge to its respiratory sound. The following factors are to be considered in the mechanism of production of auscultatory signs over a cavity: *a*, the communicating bronchus; *b*, the consistency of the wall or capsule of the cavity; *c*, the topographic relation to the thoracic wall and to the main bronchi; and *d*, the surrounding lung tissue and medium of conduction. The size and shape of the cavity also play a certain rôle in modifying the breath sounds.

The closure of a communicating bronchus may be produced by fibrosis or by secreta and necrosed material. Complete fibrosis of a bronchus is a rare phenomenon, and Dr. Auerbach, the pathologist at Sea View Hospital, tells me that he has seen only 2 cases of complete fibrosed bronchi in about 600 autopsies. However, plugging of the lumen of a bronchus by thick tenacious secretion is more common, particularly in cavities located in the outer zone of the pulmonic field (Fig. 1A), the afferent bronchus of which is of small caliber and can be easily obliterated. No auscultatory signs may be heard over such cavities, though coughing may often dislodge the plug and reopen the bronchus with consequent changes in the physical signs.

When the bronchus, communicating with the cavity, is of larger caliber, it will rarely, if ever, become plugged entirely by sputum. The physical signs of such a cavity will vary mostly with its distance from the periphery and the consistency of its walls. Fig. 1B shows a medium-sized cavity in the midzone of the third interspace of the right hemithorax. Altered breath sounds, increased whispered voice, and numerous moist râles were heard over this area anteriorly, but no adventitious sounds at all were elicited posteriorly. Stereoroentgenoscopy and Roentgen ray plates taken in the P. A. and A. P. positions, revealed the cavity to be located near the periphery anteriorly. The difference in these physical signs anteriorly and posteriorly is useful in locating the position of the cavity which is of great importance in surgical cases. This was a case of a pulmonary abscess which needed surgical intervention.

Altered breath sound and whispered voice, and particularly coarse inspiratory râles heard over a limited area in the chest, are strongly indicative of a cavity. Such cavities have a patent bronchus through which an ingress and egress of air takes place, but the walls of the cavity are soft, ragged, and not very vibratile; consequently the cavernous pitch is not produced. The capsules of these cavities are very poorly outlined on the roentgenograms, though after induction of pneumothorax, when the secretion and débris had been squeezed out from the cavernum, the walls may stand out conspicuously (Compare Figs. 2A and 2B). In a previous contribution,³ I pointed out that such cavities, if they are tuberculous

in origin, have a poorer prognosis than the absolutely mute cavities. Artificial pneumothorax is the treatment of choice of such cavities and the sooner this therapy is initiated the better the prognosis. I find these cavities to be more predominant in the caseous-pneumonic type of the clinical classification of pulmonary tuberculosis by Ornstein, Ulmar and Dittler.⁴

The relationship of the surrounding medium to the change in physical signs was studied in a large group of cases of pulmonary cavities which were treated by artificial pneumothorax. Frequent physical examinations in conjunction with serial Roentgen ray examinations have helped much in interpreting the various physical signs of a cavity. Fig. 3A shows a cavity in the right upper lobe which exhibits all the textbook cavernous signs. However, after the injection of 300 cc. of air into the right pleural cavity (Fig. 3B), the cavernous breath sounds disappeared, though whispered voice was still increased and coarse râles were heard in the subclavicular region on ordinary inspiration. Fig. C, a roentgenogram of the same case a few weeks after the initiation of the treatment, shows the cavity markedly reduced in size; the breath sounds at this time were slightly diminished, but deep inspiration and cough elicited moist râles limited to the area of cavitation. If a selective type of pneumothorax is established, the functioning portions of the lung continue to expand and contract with respiratory phases, and no adventitious signs may be heard. Normal lung tissue surrounding a small cavity may also overshadow all the auscultatory signs of a small cavity, particularly if the lung is emphysematous.

It should be stressed however, that cavernous breathing always indicates a cavity, even if the cavity is not outlined on the ordinary roentgenogram. The following case is illustrative in this respect. Cavernous signs were elicited at the right lower base, but no cavernum was visible on the roentgenogram (4A). However, on injecting iodized oil, two bronchiectatic cavities were revealed to be connected by a very small distorted bronchial canal (4B). We encountered many instances in which the stethoscope was more informative than the Roentgen ray alone.

The presence of cavernous sounds indicates as a rule, an older cavity with a thickened and well-fibrosed capsule. Such cavities are not always amenable to artificial pneumothorax, and surgical collapse is often the only means of obliterating them. The relatively silent cavities, with soft and yielding walls, can often be successfully compressed with a selective type of pneumothorax, the mechanism of which I discussed fully elsewhere.⁵ This type of pneumothorax entails very little respiratory and circulatory changes and causes little discomfort to the patient.

It is needless to say that Roentgen ray examination should be used as a routine diagnostic procedure in any suspicious case of respiratory involvement, for it always adds to our clinical under-

standing of the case. Cough or expectoration may not necessarily be complained of even in the presence of a cavity. The scope of this paper does not allow me to discuss fully the cough-reflex and expulsive mechanism of the bronchi and the reader is referred to another contribution.⁶ Suffice it to mention here that even a large bronchiectatic cavity may exist without any bronchorrhea, or tuberculous cavities situated at a distance from the main bronchi may cause no cough or expectoration. Such peripheral cavities are, as a rule, of the absolutely mute or intermediate type, for they communicate with bronchi or bronchioles of very small caliber, and may sometimes close or heal spontaneously. Serial Roentgen ray and physical examinations are essential for the determination of the proper therapeutic procedure to be carried out.

Summary. Pulmonary cavities can be divided into four groups as far as auscultatory signs are concerned. Of 350 cases of pulmonary cavities, only 104 (29.7%) exhibited cavernous breathing; 33 (9.4%) gave no inkling whatsoever as to the presence of a pulmonary lesion; 177 (50.6%) lacked the cavernous sound but manifested their presence through other adventitious signs, and 36 (10.3%) were intermediate, *i. e.*, at times were absolutely silent to auscultation and at other times revealed themselves by certain stethoscopic signs.

The factors of primary importance in the production of the variable signs of cavities are: the communicating bronchi, the consistency of the capsule of the cavity, the topographic relations, the surrounding lung tissue and medium of conduction.

The most significant and common signs of early cavitation are modified breath sounds and *localized* coarse râles heard on ordinary inspiration. Such cavities have, as a rule, soft and yielding walls which are easily amenable to collapse therapy. Cavernous breathing generally indicates an older cavity, be it tuberculous or non-tuberculous with fibrosed, rigid walls which render it refractory to medical treatment; only radical surgery is able to close completely such a cavity. The absolutely mute cavities can be diagnosed only by roentgenology; they are the least frequent and usually have a fair prognosis.

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PNEUMONIAS DUE TO PNEUMOCOCCUS TYPE VIII.*

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Department of Hospitals.)

WITH the introduction of type specific therapeutic sera it has become desirable to classify the pneumococcus pneumonias in accordance with the etiologic type and, if possible, to differentiate them clinically.

The separation of the pneumococci into specific types ultimately depends on the production of type specific antibodies as the result of their reaction with certain animal hosts. It is not unreasonable to suppose that there may be other differences in the manner in which the body responds to invasion by pneumococci of various types.

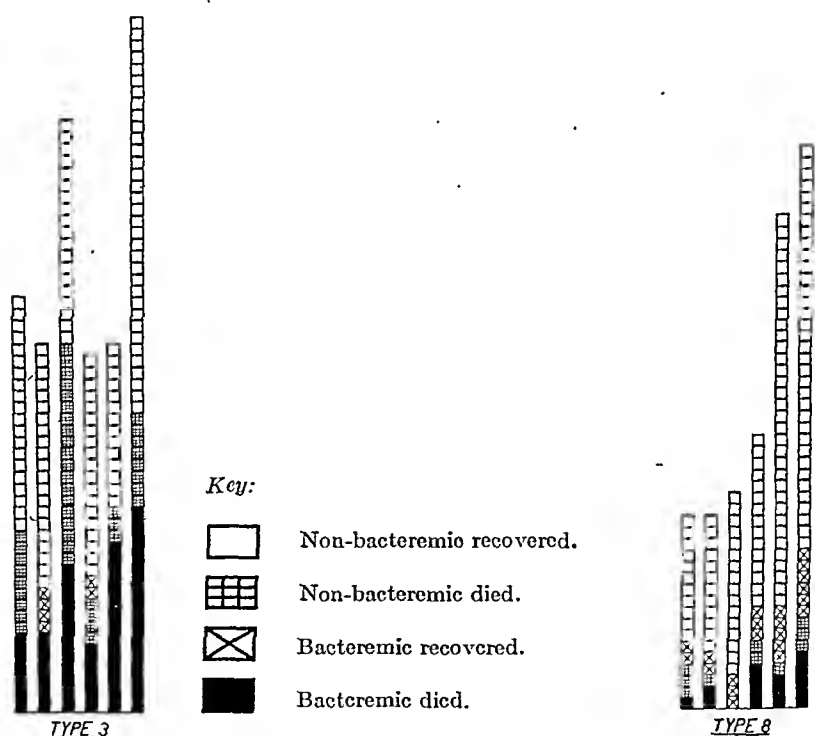
Specific differences due to the pneumococcus may exist in respect to invasion, course, symptoms and physical signs. It is our purpose to describe the reactions of the body to *Pneumococcus Type VIII*. Our studies only permit us to sketch the disease picture; details must await more extended observations. At first many cases of *Type VIII* were included with *Type III* and unless care is taken they may still be thus designated. Finland and Sutliff¹ have already furnished some data contrasting *Types III* and *VIII* in their very valuable contribution.

Frequency. We base our description chiefly on 122 cases in adults (constituting 5.9% of 2067 pneumococcus pneumonias) and 11 cases in children (constituting 2.2% of 500 pneumococcus pneumonias studied on the Pediatric Service of Dr. M. Gleich. The cases were observed during a 5-year period, July 1, 1928, to June 30, 1933. Since then we have observed more than 60 cases among adults on our Adult Service, a few on the Children's Service and several in private practice. The number of admissions to our service due to this disease has increased in recent years (Graph 1). This is not due to a transfer of cases from *Type III* to *Type VIII* because of more precise bacteriological work. It will be seen on comparing

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the two types that the number of cases of Type III has increased also.

Pneumococcus Type VIII (Cooper). In June, 1928, Sugg, Gaspari, Fleming and Neill² reported on a virulent strain of pneumococcus which is immunologically related to but not identical with typical strains of Type III pneumococci. They definitely avoided the term "sub-type" or "atypical" and referred to it as the "Thomas" strain. They showed that the Thomas strain was precipitated in low dilutions with anti-Thomas serum. In an accompanying paper by Harris, Sugg and Neill,³ it was shown that rabbits were more susceptible to the Thomas strain and mice more responsive to typical Type III.



GRAPH 1.—Annual admissions for each of 6 years, 1928-1929 to 1933-1934, of patients suffering from pneumonia due to pneumococcus Type III and to pneumococcus Type VIII.

In 1929 Cooper, Edwards and Rosenstein⁴ recovered from four strains obtained from Harlem Hospital an organism which was identical with Group IVA found by Robinson⁵ to be the most common strain of Type "IV" in 1927 in Pittsburgh, Pa., and with the Thomas strain of Sugg and his coworkers. It was suggested in this article that part of the therapeutic failures with Type III serum might be due to failure to exclude cases due to this type which the authors named Type VIII.

Differentiation. *Morphology.* In a subsequent article by Cooper, Rosenstein, Walter and Peizer,⁶ based on a study of 31 strains, the marked cross-agglutination between Type VIII and Type III was again emphasized. The capsule of Type III pneumococcus is usually much larger than that of Type VIII. Type VIII was never found to have the large mucoid colonies characteristic of Type III. There is much more hemolysis about the smaller colonies produced by *Pneumococcus* Type VIII. Cooper suggested that if agglutination and precipitation reactions are chiefly relied upon for the identity of Type III strains, Type VIII might be confused with it. She suggested that titration of strains should be made with both antisera, which she carried to high dilutions, when organisms reacting with either type are encountered.

Miss Clapp, of the Lederle Laboratories, Inc., informs me that only about 50% of rabbits, in response to the injection of *Pneumococcus* Type III, produce pure homologous agglutinins for Type III; almost one-half produce some agglutinins for Type VIII as well. When injected with Type VIII strains the rabbits rarely produce agglutinins for Type III. On this account, differentiation of Types III and VIII should be done with rabbit serum tested to contain only agglutinins for one type. Agglutination may not run parallel with "swelling" reaction. Serum which causes good "swelling" reaction should be used for the Neufeld test. All our cases of Types III and VIII for the past 2 years have been checked by Neufeld "swelling" reaction, using specific rabbit serum, a method of differentiating these two types introduced into our laboratory by our bacteriologist, Clare Wilcox. Finland and Winkler⁷ found agglutinins for the related type in patients recovering from infections with Type III and Type VIII, a finding we have had an opportunity to confirm. Occasionally both types of pneumococci have been found in the same sputum.

Errors in diagnosis of pneumococcus type can be prevented by checking, with rabbit serum, for the "swelling" reaction, all pneumococci recovered from sputum or cultures of patients or mouse blood. In our earlier work we temporarily mistyped 2 of 15 cases as Type III.

Chain Formation. *Pneumococcus* Type VIII has the tendency to occur in chains in broth cultures of the blood of mice, and exceptionally in that of patients. Chaining is usually associated with a less severe disease as if the virulence of the organisms were diminished.¹³ When found in the blood of patients chain formation should not be relied on either to foretell recovery or as a reason for omitting serum treatment because the agglutinins which produce it may disappear. The occurrence of chain formation and the fate of patients in whom the pneumococcus occurred in chains is shown in Table 1.

TABLE 1.—CHARACTER OF DISEASE IN PNEUMOCOCCUS PNEUMONIA TYPE VIII (COOPER). CASES WITH ORGANISMS IN CHAIN FORMATION, 1928 TO 1933.

Recovered from			Character of disease.
Mouse heart culture.	Lung suction.	Blood culture.	
+	Moderate
+	Moderate
+	Moderate
+	Moderate
		+	Moderate
		(1 day only)	
+	..	-	Severe
	+	..	Severe
		+ -	Fatal
		(1st) (2d)	
+	+	+	Fatal
		(Not in P.M. pericardial fluid)	

Moderate, 5 cases; severe, 2 cases; fatal, 2 cases. + = organisms in chains.
- = blood culture sterile.

The Disease as Seen in Man. There are as yet no physical criteria by means of which one can postulate with great probability that a patient who is suffering from pneumonia is infected with *Pneumococcus* Type VIII.

Invasion. In our cases the onset occurred with a head or chest cold in 23% of the cases, with a chill or chilly sensations in 75% and with pain in the chest in 89%. These symptoms were not especially severe (Table 2).

We have observed that Type VIII pneumonia patients do not, as a rule, appear very acutely ill at first. Clinicians with sufficient experience might well question a report of Type III from a patient who is not severely prostrated and request verification of the type from additional studies and fresh specimens of sputum.

Rating. In our service, cases are rated for severity in accordance with a system already published. The rating is given on admission and is significant in expressing the condition of the patient before therapeutic measures are applied. The characterization of the course, on the contrary, is intended to be an appraisal of severity, made after termination of the disease. Severe cases were fatal, or for some time had a temperature above 103.6° F. or pulse above 120 and other menacing symptoms. They had ratings below 50 at some time. Moderate cases never received rating below 50. Mild cases are those whose rating was never below 70. The relative frequency of severe, mild and moderate cases in Types VIII and III, and the mortality in severe cases, are contrasted in Graph 2. Among the Type III pneumonias there were more severe cases (42%) than there were among the Type VIII pneumonias (26%). More mild cases occurred among the Type VIII cases (47%) than among those due to Type III (15%). The severe cases were more numerous among the Type III pneumonias (42%) than among those caused

by *Pneumococcus* Type VIII (15%). Many more of the severe Type III cases (78%) died than the severe Type VIII cases (45%). Temperature always below 102° F. was observed in 5% of the Type VIII cases, and pulse below 110 was observed in 11%.

TABLE 2.—OCCURRENCE OF SYMPTOMS AND EFFECT ON OUTCOME AMONG 122 ADULT PNEUMOCOCCUS PNEUMONIAS TYPE VIII (COOPER) OF WHOM 106 RECOVERED AND 16 DIED.

	All cases with symptom.	Per cent of total (122) cases.	Fatal cases with symptom.	Per cent occurrence of symptom in all fatal (16) cases.	Per cent fatality among cases with symptom.
<i>Onset:</i>					
Preceded by cold in head or chest	28	23.0	2	12.5	7.1
Chill at onset	92	75.4	11	68.8	12.0
Pain in chest	109	89.3	15	93.8	13.7
<i>Course:</i>					
Temperature always below 102° F.	7	5.7	0		
Pulse always below 110	14	11.4	1	6.3	
<i>Symptoms:</i>					
Cyanosis	52	42.6	10	62.5	19.2
Anoxemia (requiring O ₂)	49	40.2	13	81.3	26.6
Headache	67	54.9	7	43.8	10.4
Apathy	23	18.9	3	18.8	13.0
Irritability	7	5.7	3	18.8	42.9
Sleeplessness	39	32.0	5	31.3	12.8
Delirium	18	14.8	8	50.0	44.4
Sedatives*	83	68.0	12	75.0	14.5
Hiccough	2	1.6	0		
Herpes	3	2.5			
Vomiting	25	20.5	3	18.8	12.0
Diarrhea	1	0.8	1	6.3	100.0
Distention	48	39.3	12	75.0	25.0
Icterus	2	1.6	0		
Pulmonary edema	5	4.1	5	31.3	100.0
Dehydration	5	4.1	3	18.8	60.0
Kahn positive†	28	54.9	3	100.0	10.7

* Sedatives because of pain, sleeplessness or delirium.

† Only 51 cases out of 122 cases were studied for Kahn, of whom 48 recovered and 3 died.

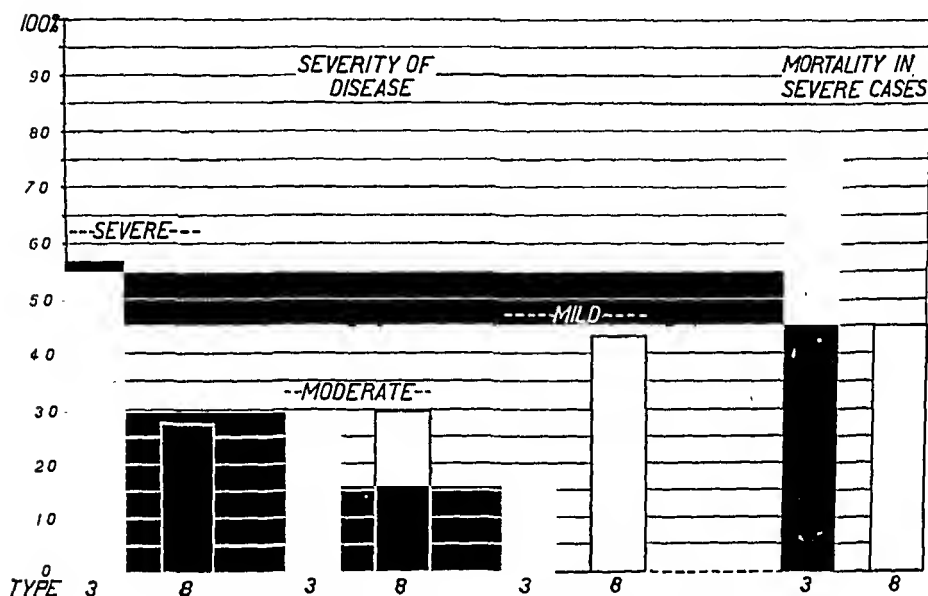
Other symptoms are listed in Table 2. Diarrhea, pulmonary edema and dehydration are seen to be of serious omen. Apparently the occurrence of a positive Kahn reaction was unimportant. It is significant that 40% of the Type VIII bacteremias occurred in mild and moderate cases. The recovery of a patient whose blood was invaded by *Pneumococcus* Type III was extremely rare.

Termination. Among the 106 cases who recovered, 32 (30.1%) terminated by crisis and 74 (69.8%) ended by lysis.

Physical Signs. The physical signs may be quite classic and well defined, involving an entire lobe. On the other hand there are

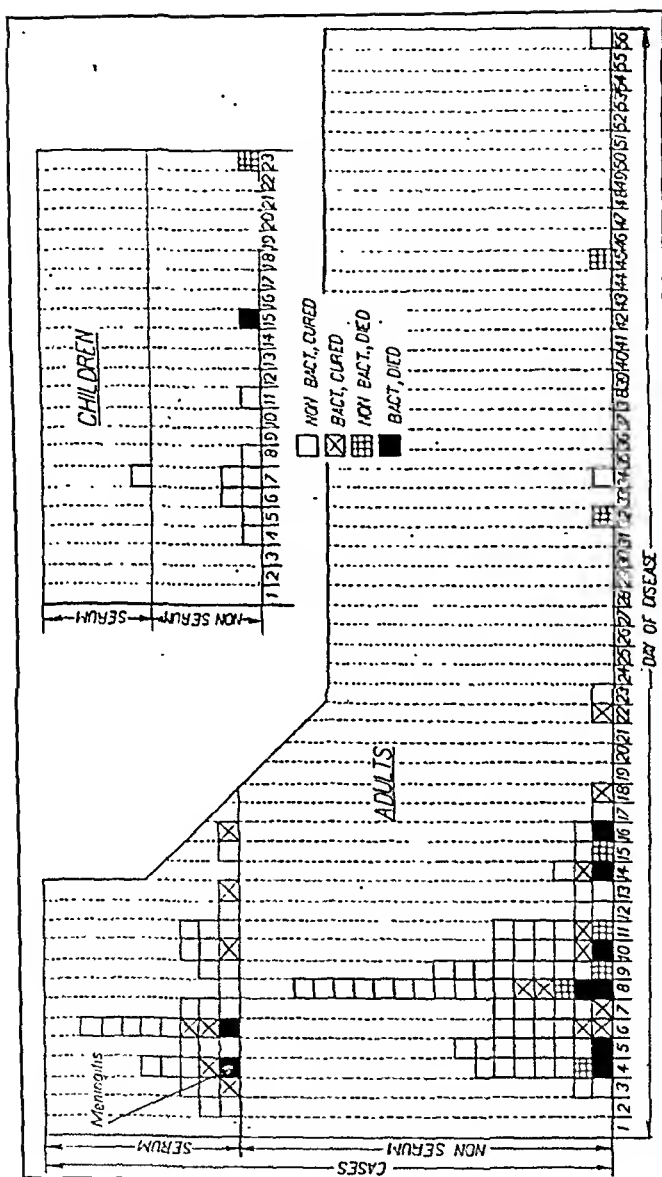
many more cases in which an entire lobe is not consolidated or the consolidation becomes manifest more slowly. There may be only slight dullness, or breathing is distant and the tubular characters not pronounced.

Roentgen Ray. The radiographs of Type VIII pneumonias frequently show involvement of part of a lobe and are less radiopaque than in pneumonias due to types with more dense consolidations, such as Type III. Type III has a tendency, not seen in Type VIII, for the pneumonia to migrate from lobe to lobe.

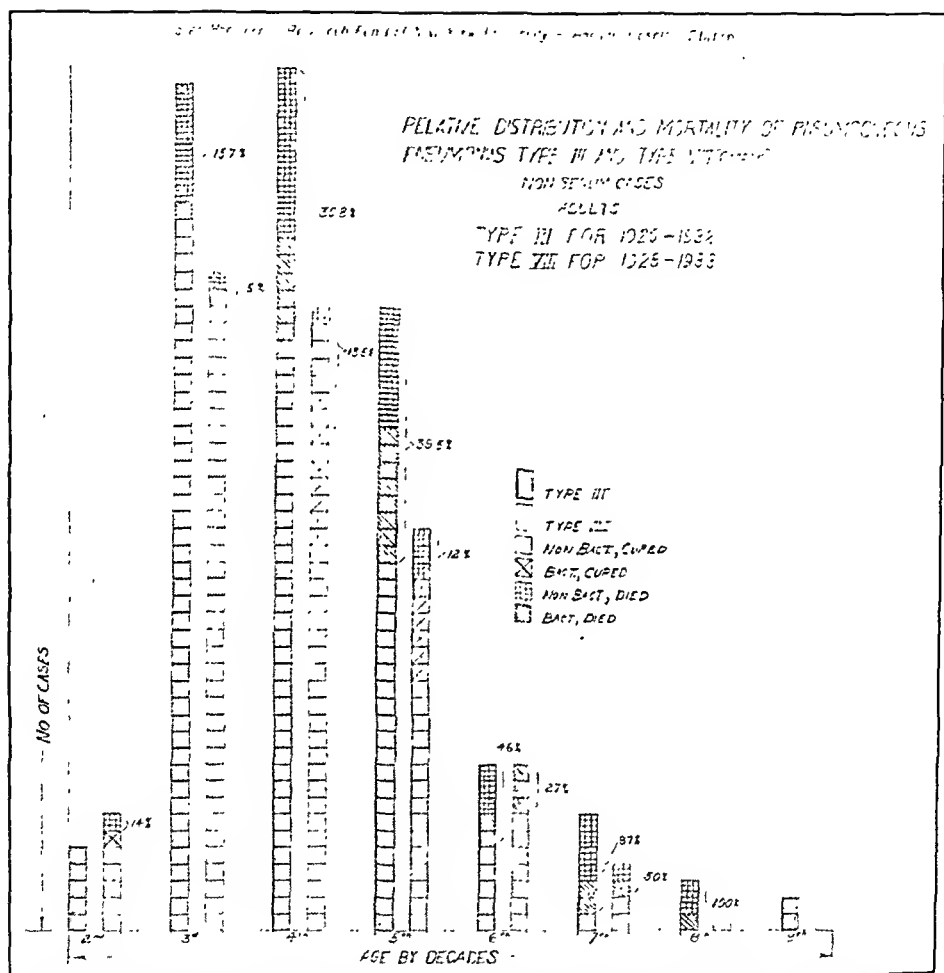


GRAPH 2.—Comparison of Types III and VIII (Cooper). Adults. Type III for 1926-1932. Type VIII (Cooper) for 1928-1933.

Sputum. Bloody or rusty sputum is encountered in pneumonia cases produced by Pneumococcus Type VIII. It is our experience that frank blood in the sputum occurs most frequently in pulmonary tuberculosis, but hemoptyses, indistinguishable from those encountered in tuberculosis, are seen in pneumonia. In the presence of consolidation and hemoptysis we must suspect, in addition to pulmonary tuberculosis, pneumonia due to either B. Friedländer or Pneumococcus Type III or Type VIII. Pneumonia due to B. Friedländer is relatively infrequent 1%, whereas pneumococcus pneumonia due to Type VIII or Type III, in the period from 1928 to 1934, constituted 22.2% of all our pneumococcus pneumonias. The frequency of the occurrence of different kinds of sputum in pneumonia due to Pneumococcus Type VIII and to Pneumococcus Type III may be compared. Rusty or bloody sputum occurred in both types in over 40% of cases but was associated with a fatal outcome in Type VIII cases much less frequently than in the case



GRAPH 3.—Day of termination and outcome. Pneumococcus pneumoniae Type VIII (Cooper). 122 adults, 11 children; 1928–1933.



GRAPH 4.—Relative distribution and mortality of pneumonias due to pneumococcus Type III and to pneumococcus Type VIII by decades. The cases in brackets with percentages were fatal.

of Type III. Suppression of sputum was of much graver significance in pneumonias due to *Pneumococcus* Type III than in pneumonias due to *Pneumococcus* Type VIII.

Pleurisy. Pleurisy occurred in 26.2% of cases (Table 3). Empyema supervened in 3 instances, 2.4%. The table also gives the relation to transthoracic aspiration of lung juice (lung suction) for diagnosis of type, to pleurisy. This procedure does not seem to have caused pleurisy or empyema, or to be associated with increased mortality.

TABLE 3.—PLEURISY STUDY OF 122 CASES IN ADULTS IN RELATION TO LUNG SUCTION.
INCIDENCE OF PLEURISY, 26.2 PER CENT; INCIDENCE OF
EMPHYEMA, 2.4 PER CENT (3 CASES).

	Cases.	Deaths.
Pleurisy without lung suction	15	1
Pleurisy before lung suction	16	0
Pleurisy after lung suction	1	0
Total	32	

Bacteremia. One of the features of pneumonia which seems to be characteristic of each type is the frequency and severity of bacteremia.⁹ Graph 8 shows the relatively low bacteremic incidence of Type III cases (12%) as contrasted with Type VIII (20%). In the non-serum cases the bacteremic mortality for Type VIII is 42%, and for Type III 100%. (The statistics for Type III include cases collected since 1926 and for Type VIII since 1928. Checks of the Sabin typing by Neufeld technique have been done for about 18 months. It is not probable that the percentages are greatly in error, as since 1928 the typings were checked by the appearance of the organisms in smears and in many cases by agglutination to titer in Type VIII antiserum in Miss Cooper's laboratory.)

The importance of bacteremia is shown when we consider the mortality experience from this angle. Among 16 fatal cases 9 had a bacteremia (56.2%) and among 106 who recovered there were only 18 with bacteremia (17%).

The degree of bacteremia, with the outcome, is given in Tables 4 and 5 for serum treated and non-serum treated cases. In the non-serum treated cases the occurrence of few organisms, as indicated by their recovery only in the broth cultures, was less fatal than when they were numerous on the plates. Two cases sterilized their blood though infected to the extent of 30 colonies or more per cc.

Duration of Cases. Graph 3 shows the duration of cases with and without serum. It will be seen that even without serum the most frequent day for termination was the eighth, and that more cases terminated on or before than after that day. With serum the termination was usually sooner than the eighth day. The days of serum administration are given in Table 6.

Agglutination Study. The day agglutination was performed and the result (stained slide agglutination technique) is given for serum

TABLE 4.—BACTEREMIA AMONG 17 NON-SERUM TREATED CASES.
BLOOD INVASION AND OUTCOME.

Sex.	Age.	Year.	Hist. No.	Out- come.	Day of disease.																	
					1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.
M.	49	1932	2750	R.	..	Br	—
M.	42	1930	4721	R.	Br	—
M.	30	1930	6367	R.	..	1 0	..	—
M.	42	1930	5874	R.	1 0	..	Br
M.	32	1931	13615	R.	Ch Br Br	—
F.	18	1928	4113	R.	Br
F.	51	1931	12305	D.	Br	Br	D.
M.	30	1931	13107	D.	—	PM Br D.
M.	50	1931	17267	D.	—	—	—	..	—	—	—	PM Br D.
M.	23	1928	3818	D.	1 7	—
M.	30	1933	30586	D.	26 28	150 152	50 46	2 2	..	Br	..	—	—
F.	32	1929	4329	R.	..	46 30	11 17	8 4	—
M.	43	1933	30341	R.	12 15	33 30	Br	..	Br	2 0	7 0	7 8	4 0	3 0	Br	..	—	—
M.	36	1928	3850	R.	55 65	6 1	—
M.	60	1933	29399	D.	Ch 2 5	..	10 14	Br	—	D.
M.	54	1932	26997	D.	116 88	D.
M.	38	1932	25548	D.	..	—	..	Br	35 50	480 500	640 284	15 5	∞ [†]	D.

— = negative culture; PM = postmortem heart blood.

* Death from Type VIII meningitis 3 months later.

∞[†] Overgrown.

Br. = broth, Ch. = chained organism, D = died.

TABLE 5.—BACTEREMIA AMONG 10 SERUM-TREATED CASES.
BLOOD INVASION AND OUTCOME.

Sex.	Age.	Year.	Hist. No.	Out- come.	Day of disease.									
					1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
F.	34	1930	3883	R.	Ch Br	— S
M.	38	1929	4443	R.	..	Br	Br	S
M.	46	1932	21818	R.	Br	S
M.	41	1931	16783	R.	—	—	1 0	—	S
M.	41	1933	29577	R.	Br	S
M.	36	1933	30525	R.	..	—	S	—	S	Br	—	—
M.	39	1933	30912	R.	25 + 51	S
M.	27	1931	14076	R.	14 + 20	..	S	..	—
M.	32	1932	4609	D.	..	400 + 500 S	320 + 300 S	D.	Meningitis					
M.	36	1932	19771	D.	1600 1760	1790 1080 S	141 *	D.

Cultures: Blood 1 cc. in broth 50 cc.; blood 1 cc. in each of two agar plates.
S = serum given on these days. * = serum exhausted. Ch = chained organism.

and non-serum cases in Table 7. Among the fatal cases there is only 1 case with agglutination present. The supply of serum was exhausted and immunity was then lost in that case.

TABLE 6.—DATA OF 37 SERUM TREATED CASES OF TYPE PNEUMONIA.

Hosp. No.	Age.	Rating.	Day of illness treated.	Units given.	Reaction.	Day disease terminated.	Outcome.
20912	39	70	5-6	46,500	Twitehing, spots before eyes	6th	Recovered
29452	28	80	4-5-6	66,000	None	9th	"
6742	29	55	8-9	87,200	None	11th	"
7323	25	65	9	24,000	Flushed (1st dose only)	10th	"
7623	38	80	9-10	60,000	None	12th	"
13892	25	40	3-4-5- 6-7-10- 11	193,000	None	11th	"
19712	51	60	96,000	Cyanosis; severe chill; elevation of temp. to 107°	11th	"
21585	50	80	5	20,000	Temp., 105°; chill	8th	"
29577	41	57	5-6	35,000	None	10th	"
30525	36	55	3-4-5	38,500	None	13th	"
14076	27	58	8-9-10- 11-12- 13	277,800	None	16th	"
4609	32	65	2-3	92,800	None	4th	Died
19771	36	60	4-5-6	136,000	Headache	6th	Died
4443	38	62	3	16,000	Nausea; severe chill	3d	Recovered
4522	39	55	2	10,400	Sweating; coughing; faintness; chill	2d	"
4660	32	80	1	8,000	None	5th	"
4745	33	78	3-4-5	24,000	None	3d	"
4807	15	80	7-8-9	172,000	None	10th	"
3883	34	50	2-3	52,000	None	3d	"
4723	47	85	2	29,600	None	2d	"
5315	28	70	5-6	58,200	Urticarial eruption, itching, pain in joints of hands, serum sickness	6th	"
6642	41	35	2-3-4- 5-6-7	235,360	None	6th	"
12956	28	75	5-6	78,000	None	6th	"
15460	22	90	4	8,000	Severe chill 2 hours later	4th	"
15880	38	70	3-5-6	105,000	Chill after last dose	7th	"
16783	41	50	4-5	24,000	None	6th	"
21818	46	85	3-4	54,800	None	4th	"
22386	43	85	4	4,000	Severe chill	4th	"
24042	36	..	8-9	36,000	None	9th	"
26288	27	60	6-7-8-9	164,000	None	15th	"
26132	25	75	4-5-6-7	40,400	Vomiting, chilly sensation, profuse sweating	7th	"
27179	13	90	5	12,000	None	6th	"
28845	23	85	2-3-4	25,000	Severe chill, perspiration	4th	"
28842	40	85	3-4	20,000	None	5th	"
16387	26	75	5-6	23,000	Skin rash	6th	"
29648	32	65	6-7	18,000	Slight chill	7th	"
30863	13	70	5	12,500	Chill	5th	"

All serum was administered intravenously.

Complications and Associated Diseases (Table 7). There were 3 cases of empyema due to *Pneumococcus* Type VIII; 2 recovered. One of these cases returned 3 months after discharge (after this

TABLE 7.—AGGLUTINATION STUDY OF PNEUMOCOCCUS PNEUMONIA TYPE VIII (COOPER) IN ADULTS.

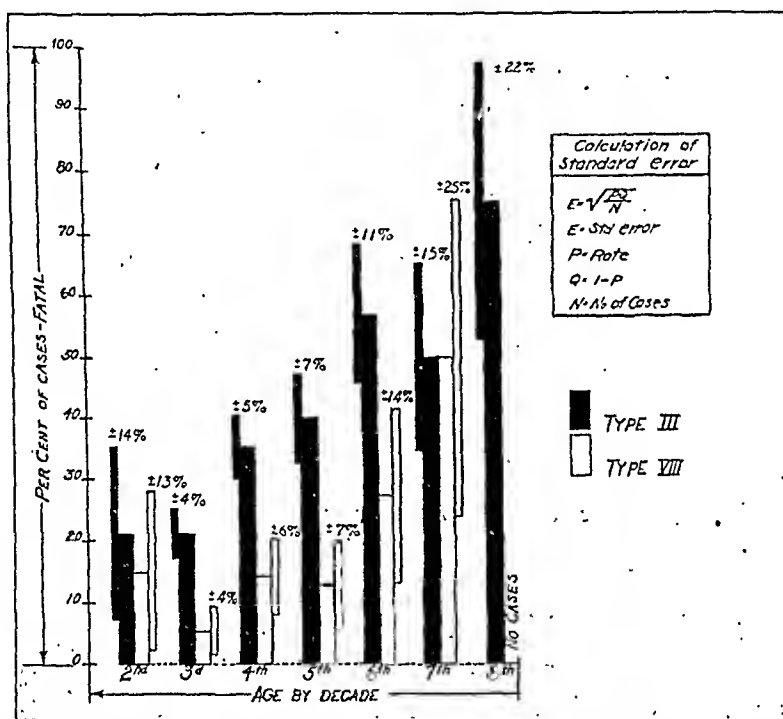
	Serum.					Non-serum.				
	Recov. cases agt. +	Recov. cases agt. -	Fatal cases agt. +	Fatal cases agt. -	Total cases studied.	Recov. cases agt. +	Recov. cases agt. -	Fatal cases agt. +	Fatal cases agt. -	Total cases studied.
Cases studied	19	8	1	1	29	11	22	0	3	36
Day of illness:										
1st										
2d		3								
3d	3	3	1				1			
4th	3	6		1		4	3			
5th	8	4		1		1	2			
6th	6			1		1	10		2	
7th	7	5					13		1	
8th	6	3				1	8		1	
9th	4	5				2	11		2	
10th	6	3					8		3	
11th	4	1				2	5			
12th	1	2				1	7			
13th	2	4				1	7			
14th	1	1				2	2			
15th		4				1	1			
16th	1	4				1	1			
17th		2				1	1			
18th		2				1	2			
19th		2								
20th	1	1					1		1	
21st	1									
22d		1					3		1	
23d	1						1			
24th	1						2			
25th							2			
26th		1				1	1			
27th		1				1				
28th		1								
29th										
30th							1			
31st										
32d	1						1			
33d										
34th	1						1			
35th										
36th										
37th										
38th										
39th	1	1	1	3	123	21	95	0	11	127
Determinations (days)	59	60	1	3	123	21	95	0	11	127

series was collected) and died of a meningitis due to *Pneumococcus* Type VIII. A fatal empyema case occurred in a patient with tuberculosis. It is our impression that *Pneumococcus* Type VIII is

more frequently encountered in the sputum of patients with pulmonary tuberculosis than pneumococci of other types.

Albuminuria. Only 4 patients showed marked albuminuria; they all recovered and the albuminuria disappeared.

Age and Sex Distribution and Mortality. Graph 4 presents the frequency of occurrence of pneumonias due to Types III and VIII, and the outcome in bacteremic and non-bacteremic cases divided into decades. It is readily seen that most of the cases of both types occurred before the fortieth year. In this graph the mortality of bacteremic and non-bacteremic cases is indicated. In Graph 5 the



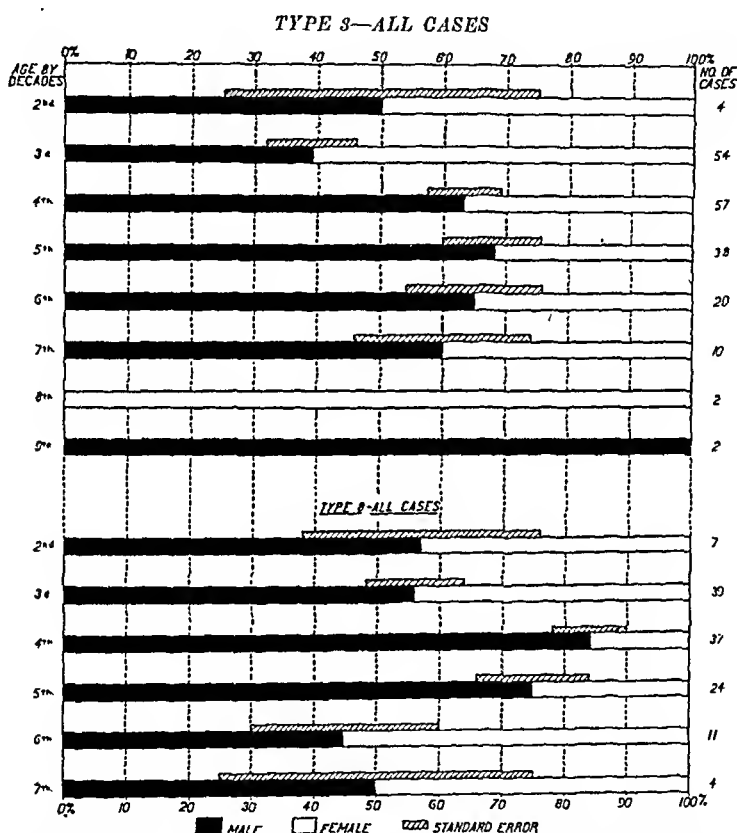
GRAPH 5.—Relative mortality rate of pneumococcus pneumonias Type III and Type VIII, according to age. Type III for 1926–1932. Type VIII for 1928–1933.

mortality is considered separately by decades for these two types. The standard error of observation is indicated by the bayonet. There is a much greater mortality in Type III than in Type VIII except in the seventh decade, where they are equal. Type III steadily increases in fatality with a slight fall in the seventh decade. Type VIII continued relatively low through five decades and then increased rapidly in the sixth and seventh.

The sex distribution is given in Graph 6. It will be seen that there is no marked selection of older females in either type and certainly the older females are not selected by *Pneumococcus* Type III as opposed to *Pneumococcus* Type VIII, as found by Blake¹⁰

and by Finland and Sutliff.¹¹ Males predominate in both types at almost all ages. This is true of many types.

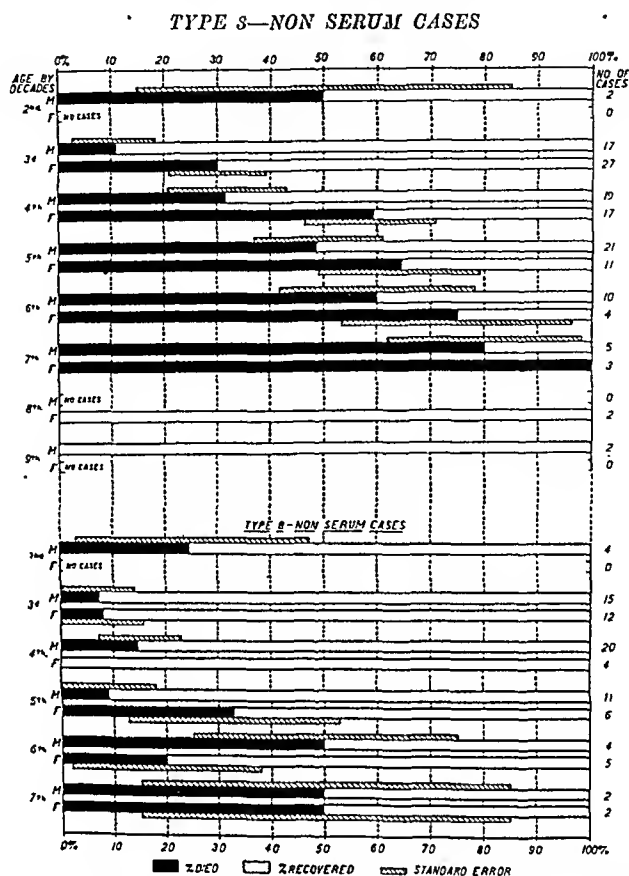
The mortality in the two types by sex is given in Graph 7. In this graph only the non-serum cases were considered so as to have an uninfluenced death rate for comparison. In all decades the female mortality for Type III is higher than the male. Only in the third decade are the cases sufficiently numerous and the difference in percentage significant.



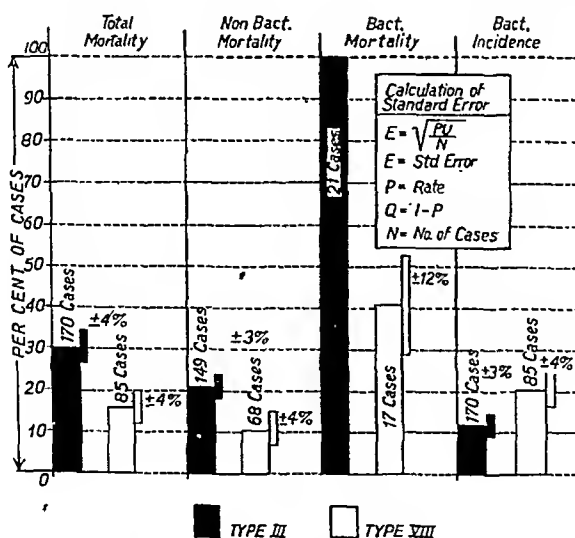
GRAPH 6.—Relative occurrence in sexes by Age. Pneumococcus pneumonias. Type III for 1926-1932; Type VIII (Cooper) for 1928-1933, all cases.

Our experience does not coincide with that of Blake or of Finland and Sutliff that older females are the chief victims of Type III. In the Type VIII cases the preponderance of female deaths does not occur. Though there are more deaths among women the error in the sampling is too large for the difference to be significant at this time.

Graph 8 shows, for the non-serum cases from 1928 to 1933, that the bacteremic mortality is less in Type VIII (40%) than in Type III (100%), and the non-bacteremic mortality is also less, 10% in Type VIII and 21% in Type III. The results are reflected



GRAPH 7.—Male and female mortality by age. Pneumococcus pneumonias. Type III for 1926–1932; Type VIII (Cooper) for 1928–1933, non-serum cases.



GRAPH 8.—Incidence of bacteremia and fatality. Pneumococcus pneumonias, Type III and Type VIII (Cooper). Non-serum cases, 1928–1933.

in the total mortality (bacteremic and non-bacteremic) which are almost twice as great in Type III as in Type VIII—30 and 16% respectively.

It is significant and fortunate that though bacteremic incidence of *Pneumococcus* Type VIII is much larger than in *Pneumococcus* Type III, the mortality is much lower in bacteremic Type VIII cases.

Therapeutic Serum. The development and use of serum for *Pneumococcus* Type VIII pneumonia has been reported elsewhere.¹² The details of the treatment, including day of illness on which treatment was given, the rating, method, day of termination and outcome, are given in Table 7. The effect of serum treatment on mortality is given in the table. The effect in shortening the disease is shown both in Graph 3 and in Table 7. In severe cases the saving of lives was striking. There were 12 cases with 2 deaths (16%) in the serum group, and 21 cases with 14 deaths (61.9%) in the non-serum group. There were 6 bacteremic cases with 2 deaths (33.3%) which received serum, and 10 cases with 7 deaths (70%) among the non-serum cases.

Children. *Pneumococcus* Type VIII is not a frequent invader of children and description of the type of pneumonia it causes must await further observations.

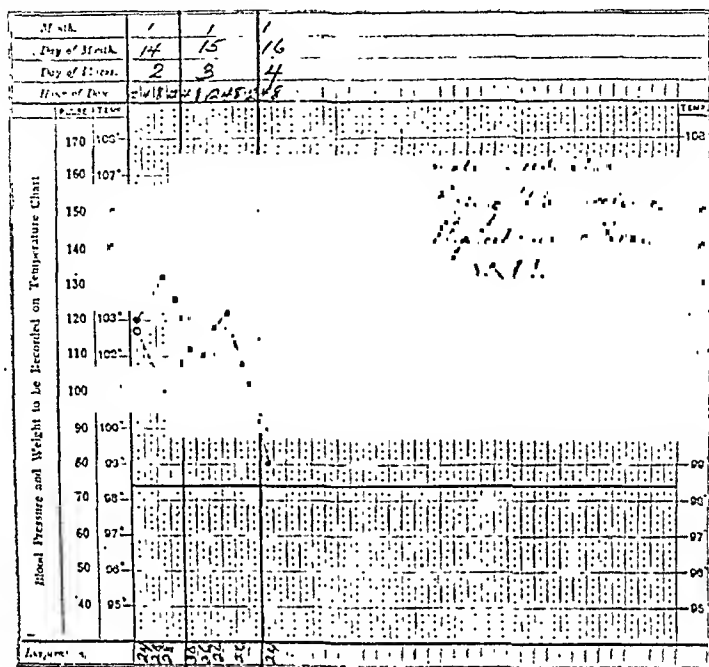
We have selected several case histories which exemplify the character of the disease.

Case Abstracts. *A Moderate Case.* H. C., a man, aged 61, was admitted to the hospital on the second day. He was rated at 65. He was icteric, with physical signs and Roentgen ray confirmation of the consolidation of the right upper lobe. His temperature and pulse were normal on the morning of the 4th day. There was considerable albumin in his urine. Case 1.

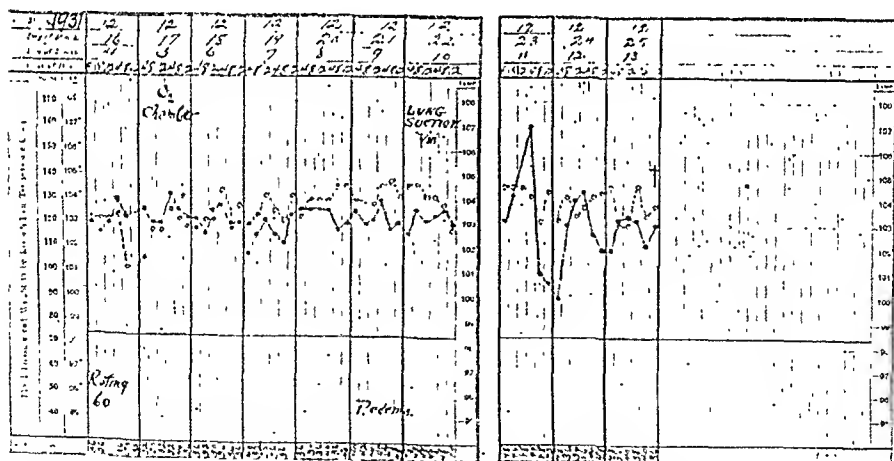
A Fatal Case. B. W., a man, aged 50, was admitted on the 4th day of his disease with a temperature of 103° F. and a pulse of 122. His respirations were 36. He was admitted to the oxygen chamber because of cyanosis and dyspnea on the 5th day. His blood count was 3100; neutrophils, 2480 and lymphocytes, 620. He continued severely ill and developed pulmonary edema on the 9th day of the disease. On the 10th day a lung suction gave *Pneumococcus* Type VIII. On the 13th day he died with pulmonary edema. His blood count was 6900; neutrophils, 5200 and lymphocytes, 1600. Case 2.

Spontaneous Pneumothorax Associated With Tuberculosis and Pneumococcus Type VIII Pneumonia. Another patient is S. W., who was admitted with a temperature of 105° F., pulse, 128 and respirations, 46. He had the signs of a pneumonia and a left pneumothorax. His white blood cell count was 25,000; neutrophils, 23,250 and lymphocytes, 1750. On the 3d day we recovered *Pneumococcus* Type VIII from the mouse heart inoculated with his sputum on the 5th day. On the 4th day the chest fluid was sterile. Tubercle bacilli were recovered in the sputum. Roentgen ray revealed a large pneumothorax with five cavities in the upper portion of the left lung, with fluid at the base and a fibrotic tuberculosis involving the right apex. On the 14th day there was pus in the left chest, which con-

tained *Pneumococcus* Type VIII. On the 27th day his condition was so poor that he required a transfusion; 16 days later he died. A thoracotomy had been performed. Case 3.



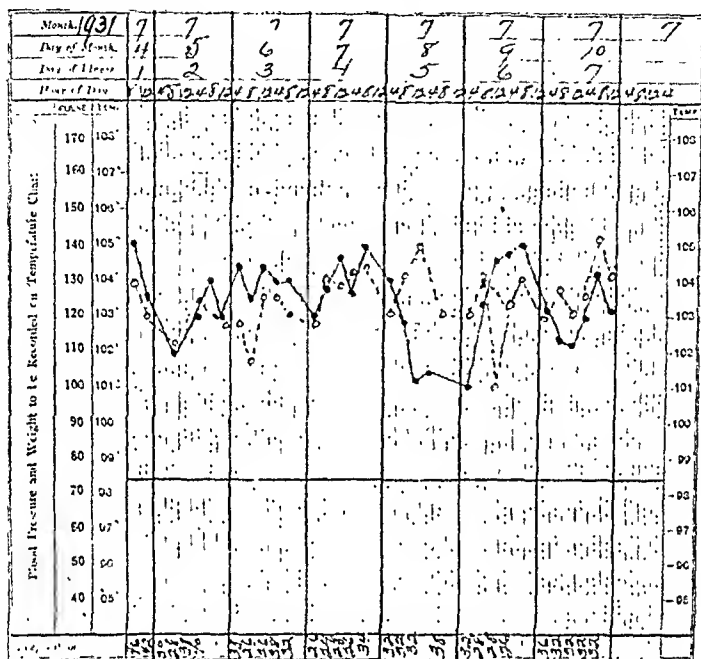
CASE 1.—Fever chart of H. C.: Pneumonia due to pneumococcus Type VIII. Moderately severe. Temperature normal on fourth day.



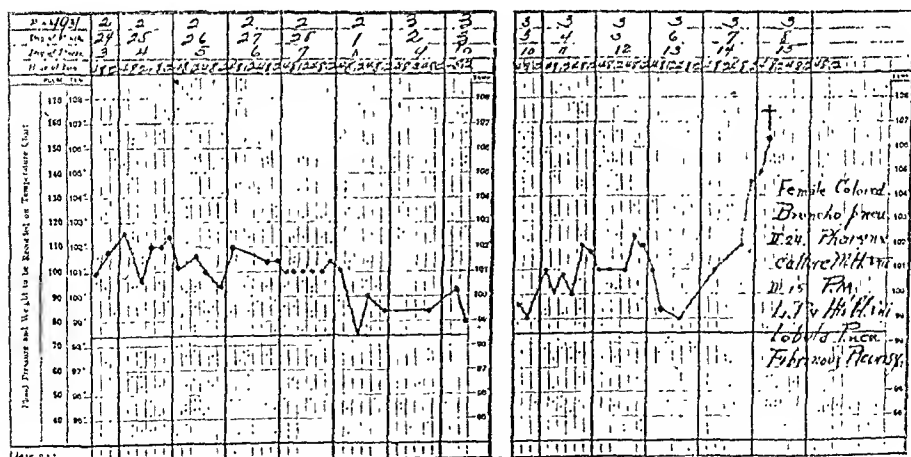
CASE 2.—Fever chart of B. W.: Fatal case of pneumonia due to pneumococcus Type VIII.

Infant With Bronchopneumonia. An infant aged 9 months was admitted with bronchopneumonia on the 3d day. Temperature fluctuated between 102.6° F. and normal until the 14th day. On that day the temperature rose to 106.2° F. and the baby died. On the 13th day the temperature had been normal. On the day of admission a pharyngeal culture was

made. The mouse inoculated revealed a Type VIII in its heart's blood. The postmortem lung suction and heart's blood of the patient contained numerous pneumococci Type VIII. The autopsy revealed a lobular pneumonia and a unilateral fibrinous pleurisy. This case exemplifies the occurrence of partial immunity which is later lost. This seems to be frequent in invasions by this pneumococcus. Case 4.



CASE 3.—Fever chart of S. W.: Pneumococcus pneumonia in patient with pneumonia due to pneumococcus Type VIII complicated by pyopneumothorax. Onset with spontaneous pneumothorax.



CASE 4.—Fever chart of infant with bronchopneumonia due to pneumococcus Type VIII.

Late Complication. A non-serum case cleared his blood stream, had an empyema, operation and was discharged as cured. Three months later he returned with a pneumococcus Type VIII meningitis, and died. Case 5.

TABLE 8.—COMPLICATIONS AND ASSOCIATED DISEASES AMONG 122 ADULT CASES.

Complication or associated disease.	No. of cases.	Bacteriology and remarks.	Outcome.	
			Recov- ered.	Died.
Empyema	4	1 hem. strep. after Type II (sec- ondary infection)	1	
(No lung suction on these cases)		3 pneumococcus Type VIII*	2	1
Meningitis	1	Pneumococcus Type VIII	..	1
Otitis media	1	Not due to pneumococcus Type VIII	1	
Nephritis	4	Marked albuminuria	4	
Epilepsy	1	1	
Emphysema	1	1	
Paget's disease	1	1	
Miscarriage	1	1	
Alcoholism	1	1	
Delirium tremens (alcoholic) ..	1	1	
Obesity	1	1	
Small fibrotic tuberculous lesion in right intraclavicular region	1	Tubercle bacilli not found in sputum	1	

* The 2 cases who recovered were operated; the fatal case was operated, had a spontaneous pneumothorax with a tuberculosis, and had positive sputum.

Summary. Based on 122 cases in adults and 11 cases in children, a rough sketch of the disease produced by *Pneumococcus* Type VIII is given. It is usually of less severity than the disease produced by some of the other pneumococci. It is much less serious than pneumonia due to *Pneumococcus* Type III. The organism invades the blood more frequently than does *Pneumococcus* Type III, but with a much smaller mortality. It produces bloody sputum frequently. Occasionally it may be associated with pulmonary tuberculosis. It is treacherous, invading the meninges or the blood stream after apparent subsidence of symptoms. This may be due to the development of a focus which subsequently ruptures and releases virulent organisms. When organisms recovered from the sputum occur in chains the cases are, on the average, less severe. When in cultures of subsequent sputa or blood the chaining disappears, the organisms are virulent or resistance has been lost. The organisms do not invade the older age groups with especial frequency. The age distribution is similar, in our experience, to that of Type III, except that the latter is more frequent in children. Agglutinins are formed and can be readily transferred in therapeutic serum. When demonstrable agglutinins do not develop the patients are less apt to recover.

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GIARDIA INFESTATION OF GALL BLADDER AND INTESTINAL TRACT.

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THE flagellated protozoön *Giardia intestinalis* was first observed and vividly described by Leeuwenhoek.¹ In the course of subsequent studies it has been variously named *Cercomonas intestinalis* (Lambl²), *Dimorphus muris* (Grassi^{3,4}), *Megastoma entericum* (Grassi^{4,5}), *Giardia* (Künstler⁶), *Lambia* (Blanchard⁷), and *Lambia duodenalis* (Stiles⁸). Kofoid and Christiansen⁹ consider the terminology *Giardia lambia* correct, but Lambl's original specific name *intestinalis* persists, and the organism is most frequently referred to as *Lambia* or *Giardia intestinalis*.

The pathogenic rôle of this parasite is still in dispute. Experimental data are meager, and autopsy reports almost non-existent. The following case, therefore seems worthy of report, particularly since the infestation was associated with chronic inflammation of the gastro-intestinal tract and since, at autopsy, the gall bladder was found to be teeming with the invading organisms.

Case Report. J. S., No. 9391, a 57-year-old blacksmith and farmer, was admitted November 15, 1931, for the relief of diarrhea. No other member of his large family was similarly affected. With minor exceptions, his past health had been good. He had never had skin lesions of any kind, nor had his tongue been sore. His teeth had been in poor condition for many years. He had long had a tendency to constipation. There had been no clay-colored or tarry stools. Nycturia (2 or 3 times a night) had been present for many years.

His digestive complaints had begun 16 years previously, with intense burning and sense of fullness in the epigastrium with occasional nausea and vomiting from 10 to 30 minutes after eating. The vomitus is said to have contained undigested food and dark brown blood. At first these symptoms were all relieved by alkalin drugs, but more recently such medication was not effective. Heavy foods such as meats and vegetables made his symptoms worse, and he consequently had limited his diet to soups, eggs, and milk.

Five years before admission his symptoms became so severe that he had to give up his work as a blacksmith, and since that time he had done no hard labor. During the 2 years before admission there was a rapid increase in severity of the symptoms, with loss of weight and weakness so marked as to cause occasional fainting spells. For 14 months preceding hospitalization he had been able to retain only the smallest amounts of liquid food and eggs.

Five days before admission a profuse diarrhea set in, with 10 or 15 dark, liquid stools a day, and he became so weak that hospitalization was imperative.

Physical Examination on Admission. Temperature 37° C., pulse 98, respirations 16, blood pressure 130/95. He was in no acute distress, but appeared tired and chronically ill. The skin was rather dry; the mucous membranes were of good color. There was no generalized lymph node enlargement. Hearing was somewhat impaired, bilaterally. *Eyes:* There was marked impairment of vision, slight anisocoria, and almost no pupillary response to light. Ophthalmoscopic examination showed marked thinning and increased light streak of the retinal arterioles, normal cupping of the disks, and no retinal exudates or hemorrhages. *Mouth:* Teeth were in very bad condition, with several extractions, considerable caries, and marked pyorrhea. The tongue was slightly reddened around the edges only. *Neck* showed no abnormalities. Except for a few râles over the larger bronchi in the right interscapular region the lungs were normal. The *heart* was not enlarged to percussion; the heart sounds at all areas were very distant and were of poor muscular quality at the apex; the second aortic sound was somewhat increased. The abdomen was diffusely rigid; no masses could be felt; lower abdominal scars were present, the result of previous herniorrhaphy. The *genitalia* were normal. *Rectal* examination seemed to cause considerable pain although there were only a few hemorrhoidal tags to account for it; the prostate was slightly enlarged but contained no masses and was not indurated; there were no abnormal masses in the rectum. The *reflexes* and *neurologic examination* were normal.

Accessory Examinations. Red blood count 4,250,000; hemoglobin 14 gm. % (Sahli); white blood count 19,550; neutrophils 75%; small lym-

phocytes 12%; large lymphocytes 9%; monocytes 4%. The urine was entirely normal. The blood Wassermann reaction was negative. Blood chemistry examinations showed a carbon dioxid combining power of 53.2 volumes%; non-protein nitrogen 47 mg.%; sodium chlorid 386 mg.%. Repeated bacteriologic study of blood and stools showed no abnormal findings.

Roentgen-ray examination of the gastro-intestinal tract revealed nothing unusual in the stomach or duodenum. The colon had practically emptied 24 hours after the barium meal. Barium enema revealed very marked spasm of the lower descending and sigmoid colon, but the barium passed readily into the other parts of the colon. The cecum was rather small and easily movable. There was loss of the haustral bands distal to the splenic flexure. The roentgenologist was of the opinion that the evidence favored some form of colitis that had been present long enough to produce thickening of the colon wall and that was causing considerable spasm at the time of examination.

Analysis of the *gastric contents* showed many red blood cells and a positive guaiac reaction but no undigested food, Boas-Oppler bacilli, or other evidence of gastric retention. There was no free hydrochloric acid in the stomach contents even after histamin stimulation.

The *vomitus*, examined thrice, consisted of clear liquid and food particles, without gross, microscopic, or chemical evidence of blood. On one occasion it was swarming with actively motile *Giardia*.

The *stools*, which were examined frequently, were liquid, brown, and bloody, with a moderate amount of mucus. Microscopic examination showed many red blood cells, and the guaiac and benzidin tests were strongly positive. On the third day after admission, many motile *Giardia* were observed; afterward, only encysted forms were found in the stools.

Course in the Hospital. For the first 6 days, the temperature remained normal, although there was an occasional tachycardia. During this time, the patient had from 5 to 7 stools a day. His appetite was poor, and he vomited several times daily. On the 7th day, he became much worse. His diarrhea increased, his temperature rose to 38.6° C., and he appeared much weaker. He refused food and fluid; glucose and saline had to be administered parenterally. All attempts to check the diarrhea, including large doses of opiates and calcium, were futile. In view of the presence of *Giardia* in the intestinal contents, one dose of neoarsphenamin (0.45 gm.) was administered, without apparent effect.

From this time on, his course was rapidly downward. His diarrhea increased to as many as 20 stools a day, his appetite failed entirely and he became so weak as to be almost helpless. In spite of all treatment he died on the 12th day after admission.

Autopsy (7½ hours after death). The salient features were as follows: The body was that of a well-developed and moderately well-nourished white male. The visceral and parietal *pleurae* of both lungs were bound together by old fibrous adhesions, which were more diffuse over the left lung. Both *lungs* contained a small amount of fluid and areas of thickening of the interstitial tissue. The *liver* weighed 1825 gm. Its external surface was smooth. It contained a tumor, 1.5 cm. in diameter, which was made up of many small bloodvessels. The liver also contained a large amount of fat, which, however, was not distributed in any characteristic pattern. There was an increase in the number of mononuclear cells about many of the portal canals.

The *gall bladder* was normal in size, and contained a brownish-black, mucoid secretion. Some of this secretion, before the gall bladder was opened was found to be teeming with *Giardia*, most of which were in the vegetative stage. The wall of the gall bladder was partially autolyzed,



FIG. 1.—Superficial ulcers and atrophy of the mucosa in the sigmoid colon in a case of *Giardia* infestation of the intestinal tract.

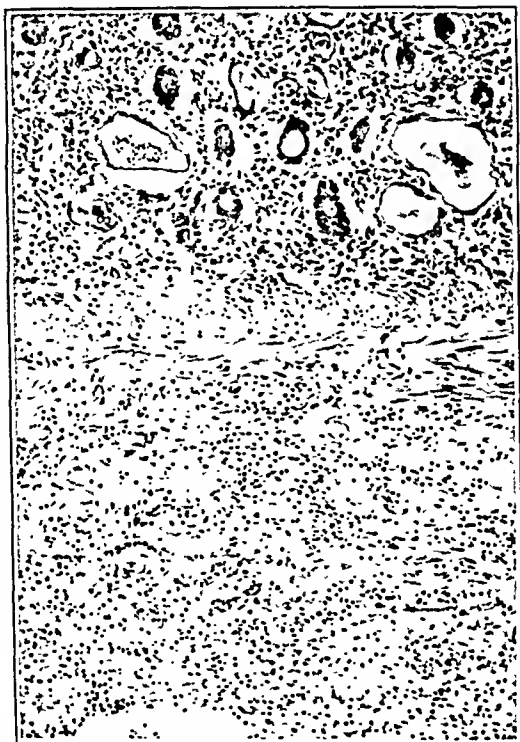


FIG. 2.—Photomicrograph of a part of the colon near one of the ulcers shown in Fig. 1. The inflammatory reaction is pronounced in the submucosa.

and a few mononuclear cells could be seen in portions of the wall. However, no *Giardia* could be demonstrated in section. The bile ducts were patent and normal.

The spleen weighed 225 gm. and was relatively soft, resembling a mild acute splenic tumor.

The lesions of greatest interest were found in the *intestinal tract*. The lumen of the distal half of the transverse colon and of the descending and sigmoid colon was dilated. The entire tract showed evidence of a chronic inflammatory process in the mucosa and part of the submucosa, these changes being most pronounced in the colon. The mucosa of the colon was atrophied in some areas, while in other areas there were superficial ulcers, some in small clusters, others distributed in a line along one of the *tæniæ coli*. The margins of these ulcers were ragged and hemorrhagic and the bases slightly necrotic. The largest ulcer, which was located 8 cm. from the anal margin, measured 6 or 8 mm. in diameter and extended down into the muscularis. In addition to the ulcerated areas in the colon, portions of the mucosa were covered by a diphtheritic membrane. In the ulcerated areas there were many Gram-positive and Gram-negative bacteria, the predominating organism being a Gram-positive, elongated diplococcus. No *Giardia* were found.

Discussion. Pathogenicity. The question of whether or not *Giardia* is pathogenic for man is still undecided, opinion being about equally divided. Wenyon,¹⁰ Fantham and Porter,¹¹ Lyon and Swalm,¹² Smithies,¹³ and Heubner¹⁴ are of the opinion that it may cause clinical symptoms; but Boeck¹⁵ takes the position that the arguments so far presented are not conclusive.

Experimental observations are few, but in the main, as for example in the work of Deschiens¹⁶ and of Fantham and Porter,¹¹ the evidence seems in favor of their being truly pathogenic, although Boeck¹⁵ points out pertinent objections to certain of the experiments.

Autopsy reports likewise fail to solve the problem, because infestation with this organism is apparently rarely fatal. We have been able to find only one autopsy report on this subject, that of Fairise and Jannin.¹⁷ The clinical history was that of chronically recurring diarrhea. Necropsy showed numerous discrete and confluent, fungating ulcers in the cecum, ascending colon, and, to a less extent, the descending colon. These authors also made the significant observation that *Giardia* is not only a surface parasite but may penetrate even to the subserosal coat. They conclude that the organism is pathogenic.

The evidence in our case is by no means conclusive, for *Giardia* could not be demonstrated in the intestinal wall even at the site of the ulcers. It is possible, moreover, that the patient's grossly deficient diet was the primary cause of his symptoms, and that the parasite was merely a secondary invader in an intestinal tract already injured as a result of chronic avitaminosis.

Relation to Gall Bladder Disease. Whether or not *Giardia* may give rise to chronic inflammation of the gall bladder is likewise a disputed point. Suspicion has been cast in its direction especially since the introduction of the Meltzer-Lyon method of duodenal

drainage. The literature contains reports of numerous cases in which duodenal aspirates, negative under fasting conditions, yielded large numbers of *Giardia* after magnesium sulphate stimulation. This evidence, however, is open to the possible objection, suggested by Boeck, that the flagellates may have been driven out of the glandular crypts by the irritant action of magnesium sulphate.

More trustworthy evidence of their invasion of the gall bladder has been adduced by finding the parasites at operation (1 case by Westphal and Georgi¹⁸ and 2 cases by Smithies.¹⁹). So far as we have been able to find, ours is the only case in which *Giardia* have been demonstrated postmortem in the gall bladder.

It cannot be claimed, of course, that the mere presence of *Giardia* in the gall bladder is proof of their pathogenicity. But the fact that they have been found in this organ at operation and now at autopsy makes it fairly reasonable to assume that their demonstration in duodenal aspirates is indicative of their presence in the gall bladder; and it may well be that their invasion could give rise to symptoms of gall bladder inflammation. Further clinical, operative, and autopsy observations will of course be required before their true significance can be determined with accuracy.

Summary. A case is reported of a 57-year-old blacksmith who for 16 years had suffered from intestinal discomfort, consisting at first of epigastric fullness and burning, and progressing to vomiting, loss of weight and strength, and finally severe diarrhea. All studies were normal, except that the stools were teeming with motile *Giardia*. These organisms were observed also in the vomitus.

Autopsy revealed a diffuse enterocolitis with atrophy and hyperemia of the mucosa of the duodenum and large intestine, and, in addition, numerous superficial ulcers in the colon. *Giardia* were present in the gall bladder bile removed at autopsy.

The possible pathogenicity of this organism and its relation to gall bladder disease are discussed.

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LONG-CONTINUED VACCINE THERAPY AS A CAUSE OF AMYLOIDOSIS.

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AMYLOID disease has long been known to be associated with chronic infection, malignancy and more recently with multiple myeloma.¹ Since the latter diseases are frequently accompanied by disturbances in the blood protein levels, especially by an increase in the normal or abnormal globulins it would appear that this common factor is involved in the formation and deposition of an abnormal protein called amyloid substance. Although other factors, such as disturbance of the reticulo-endothelial tissue, may also play a rôle, the experiments of Kuczynski,² in which amyloid disease was produced in mice simply by feeding large amounts of casein, seem to show that excess of protein alone may give rise to the disease in certain cases. Other clinical and experimental studies have shown that the blood proteins may be increased by a high protein diet. Our own experiments to be published elsewhere support the idea that amyloid disease frequently follows long periods of hyperglobulinemia. Four rabbits were given approximately 96 intramuscular injections of sodium caseinate over a period of 8 to

13 months. During this time the amount of blood globulins was increased from 2 to 4 times over the normal level. Each of the animals died from extensive amyloid disease.

In 1899 Paltauf³ noted amyloidosis in horses inoculated repeatedly with antigens for the production of serums. Similar observations have been made subsequently, the most recent by Sipos⁴ who found amyloidosis in 80% of the horses used for the production of various serums and vaccines, and by Doerken and Arndt⁴ who found the condition in 60% of horses used for similar purposes. Amyloid disease has been deliberately produced in various animals by the repeated injection of a variety of bacterial vaccines, toxins, casein, egg albumin, gelatin, nuclein, zein, peptone, organ transplants, silicates, manganese chlorid, sulphur, selenium, turpentine and other substances.⁵ The literature covering these experiments up to 1918 is summarized in the papers of Bailey and Hirose.⁶

Langstein and Mayer⁷ in 1904 showed that vaccines when injected into animals led to an increase of blood proteins, especially of the globulins. Similar observations were made subsequently both in animals and in man after the injection of a variety of substances.⁸ There is evidence to suggest that the blood proteins are normally formed by various widespread tissue cells.⁹ Under the abnormal stimulus of the disturbance which follows parenteral injection of a variety of substances, by infections or neoplasms, the rate of formation is hastened, thereby increasing the amounts of blood proteins over the normal. It is believed that amyloid substance may be the result of the deposition or precipitation in the tissue of the excess amounts of normal globulins¹⁰ or of new abnormal proteins¹ produced under these circumstances.

These facts supported by the discovery of amyloid substance in vaccinated animals, the increase of blood globulins in patients with amyloid disease¹¹ and by our own unpublished experiments showing a constant hyperglobulinemia in rabbits which ultimately died from amyloidosis, suggest a causal relationship between conditions causing chronic hyperglobulinemia and eventual amyloid disease. With these possibilities in mind there is reason to believe that repeated injections of vaccines or a variety of other substances commonly used for therapy in man may in some individuals be the underlying cause or contributing factor in the formation and deposition of amyloid substance. The following case report illustrates this possibility.

Case Report. Mr. L. L., aged 28, had typhoid fever at the age of 7, pneumonia at 9, chickenpox at 11, smallpox at 14 and dysentery at 19.

In 1925 he noted soreness in the right arm after exercise and gradual stiffness of the shoulder. By 1927 the shoulder was completely ankylosed. In 1929 his left knee became red, swollen and tender 2 days after slight trauma. Following this there was gradual limitation of movement of his left shoulder. By February, 1931, the arthritis had progressed so that crutches were necessary. In March, 1931 an autogenous vaccine was made

from organisms said to have been recovered from the fluid aspirated from the knee. He was given 9 intramuscular injections during the following 3 months. In August he was given an intravenous injection of streptococcus vaccine and was admitted to the Medical Service as a bed patient in September. Between September and March, 1932, 20 intravenous injections of streptococcus vaccine were given at weekly intervals. There was continual fever ranging from 37.2°C (99°F) to 37.8°C (100°F .) during the period of vaccine therapy. His condition improved slightly. On subsequent visits to the Out-patient Department he received 2 more vaccine injections. During July and August, 4 injections were given by his own physician, and in October he received 3 more from another physician.

In November, 1932, blood and mucus appeared in his stool. In December, he vomited much of his food and was jaundiced for 2 weeks. In January there was repeated transient swelling of the eyelids and ankles. His physician then administered 3 more injections of streptococcus vaccine intramuscularly. He improved somewhat but in September, 1933, he vomited most of his food and drink. His temperature was said to have been subnormal 35.6°C . (96°F .). Bloody diarrhea appeared and blood oozed from his nose. In October, 1933, he was readmitted to the hospital with the usual signs and symptoms of uremia. His blood pressure was 107/60, blood urea nitrogen 147 mg. per 100 cc. There was heavy albuminuria and marked anemia. Amyloid disease was suspected although the liver and spleen were not palpable. This impression was confirmed when all of the 200 mg. of Congo red dissolved in distilled water and injected intravenously was absorbed by the tissues in 60 minutes. The blood proteins totalled 4.71 gm. per cent composed of 1.29 gm. fibrinogen, 2.67 gm. globulin, and 0.74 gm. albumin. The patient became comatose, developed pericardial friction and edema of the lungs and died in November, 1933.

NECROPSY (Dr. R. W. Koucky): The chief relevant findings were marked amyloidosis of the spleen, liver, kidney and adrenals and the lesions of chronic arthritis. The spleen and adrenals were bright pink due to staining of the amyloid substance by the Congo red injected intravenously on the preceding day. The iodine-sulphuric acid test showed large bluish blotches of amyloid substance in the liver, spleen, adrenals and kidneys. Practically all of the renal glomeruli were infiltrated with amyloid substance. The spleen and liver showed generalized amyloid infiltration. Deposits of amyloid in the adrenals were limited to the cortices. The right knee joint contained clear, slightly turbid, sterile fluid. There was hypertrophy of the synovial membrane with atrophy of the cartilage on the femoral and tibial surfaces. Here and there were projections of bone suggesting hypertrophic changes. Section of the adjacent bone showed thinning out due to atrophy. The right shoulder joint cavity was largely obliterated by bony ankylosis. No cartilage could be recognized, the whole area was atrophic. The bone adjacent to the joint was thin and could be broken with the fingers.

Comment. This evidently was a patient with chronic rheumatoid or infectious arthritis to whom at least 41 injections of vaccine were given at more or less regular intervals over a period of 22 months. The number and spacing of the injections corresponded generally to those given to animals in which amyloid disease developed in a high percentage of cases. Arndt and others noted in horses that amyloid substance appeared between 8 and 16 months after the first injection of vaccine. The question was raised as to whether the arthritis itself, the vaccine therapy, or a combination of the

two was responsible for the development of amyloidosis in the present case. Because of the rarity of reports¹² of amyloid disease associated with a disease as common as arthritis and the regularity with which parenteral injections of a variety of substances produces amyloidosis experimentally, it would seem that the long-continued vaccine therapy was at least an important factor if not the actual cause in its development. The possibility of amyloidosis as a sequela to parenteral shock therapy was suggested by Letterer.¹⁰ Doubrow,¹³ in discussing a paper regarding amyloid disease in a tuberculous patient who had received gold injections, also suggested the possibility of a relationship between the therapy and amyloid disease. As far as we are aware, however, the case described here is the first reported in which evidence points strongly to prolonged vaccine therapy as a cause of amyloid disease.

Although recognized amyloidosis seems to be a rare sequela of vaccine therapy it is important to bear the possibility of its occurrence in mind and to discontinue injections upon the appearance of the first evidence of the disease. It is known that amyloid substance produced experimentally may be resorbed if the cause is removed before the disease is too far advanced.^{2,14} Furthermore, numerous recorded cases of recovery from amyloid disease¹⁵ indicate that the disease is not always fatal, provided the cause be removed in time.

Summary. A patient suffering from chronic arthritis was given 41 injections of vaccine over a period of 22 months. During this treatment amyloid disease developed and the patient died. Because of the rarity of the occurrence of amyloid disease in chronic arthritis and the frequency with which it occurs following long-continued parenteral injection of numerous substances including vaccine, it was believed that vaccine therapy was responsible for amyloidosis in this case, the first that we know of to be so described.

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THE INFLUENCE OF MUSCULAR ACTIVITY ON PHYSIOLOGIC LEUKOCYTOSIS.

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BLOOD leukocytes are part of the vast migratory cell population of the body. Their increase during infection is well known. There are also less extreme but nevertheless definite hour to hour variations, termed physiologic leukocytosis. Many investigators have correlated these variations with environmental changes, with various phases of metabolism and with psychic activity. The sources of the extra white blood cells also have been investigated and the pathways by which they are mobilized.

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The experiments reported in this paper are concerned chiefly with the difference in the effect of motion and emotion in rapid leukocyte mobilization, and are grouped as follows: 1, Combined excitement and muscular effort; 2, excitement alone; 3, effect of anesthetics on white blood cells; 4, muscular effort without excitement (under anesthesia); 5, the effects of exposure to cold.

Materials and Methods. Cats were chosen because they are easily aroused to excitement, a generalized sympathetic discharge can be clearly demonstrated, and their blood picture is comparable to that of humans. Over 50 experiments were performed on 21 clinically normal animals.

A standard hemacytometer (Thomas) and diluting pipettes all passed by the United States Bureau of Standards were used.

Blood films were made on slides and stained by Wright's method. Two hundred cells were counted on each slide, counting from edge to edge of the slide. The large and small lymphocytes and mononuclears were all classed as round cells, without further differentiation.

The blood samples were obtained from a marginal vein of the ear, following incision with a sharp knife. All blood samples were taken from a freely flowing drop. Samples were in all cases counted by the person who took them. Usually they were done by one of us; all differential counts were done by one man (C. J. L.).

Variations in total count of less than 1000 cells were regarded as within the limits of experimental error, and therefore insignificant.

A complete experiment usually continued for 1 to 6 hours (average 3 hours) during which time from 3 to 13 samples were taken. The number of samples depended upon the information desired and the type of experiment.

The anesthetics used were ether, given by the open cone method, and sodium amytal (Lilly) administered intramuscularly. The usual dose of amytal was 70 mg. per kilo of body weight.

Excitement with muscular work was obtained by tying the animal on an operating board and allowing it to struggle.

Passive exercise under anesthesia was obtained by supporting the animal on a specially designed constant-speed electric treadmill made by Mr. Victor Phillips in the Department of Anatomy machine shop.

Excitement without muscular work was obtained by riding the animal in a high-speed elevator. All of the animals showed fear, evidenced by crying, dilatation of pupils, and erection of hair. They were placed on the floor of the car without restraint and only those which remained motionless were classified under this category. Observations on those which showed any muscular response, or which tried to escape, were discarded or included under the heading of excitement plus muscular work. The minimal muscular response is a point of importance, which will be emphasized elsewhere.

The experiments listed here are those in which the total count sequences are complete and which have been carefully checked. Many incomplete observations have been omitted for the sake of brevity, but the results are essentially the same as those reported.

Results. *Effect of Muscular Work During Excitement.* Excitement induced responses which varied from mere restless moving around to violent struggling. There were 9 experiments on 6 animals. The total white count rose in all cases. Of these, one was insignificant, and another was discarded because a large number of circulating normoblasts vitiated the counts. The elevations in

total count varied from 5% to 30% with an average rise of 22.7% in 17 minutes. The rise was purely mononuclear in type in 3 cases, mononuclear and neutrophil in 2 cases, pure neutrophil in 1 case, not determined in 3 cases. Excitement with muscular activity increases the total white cell count.

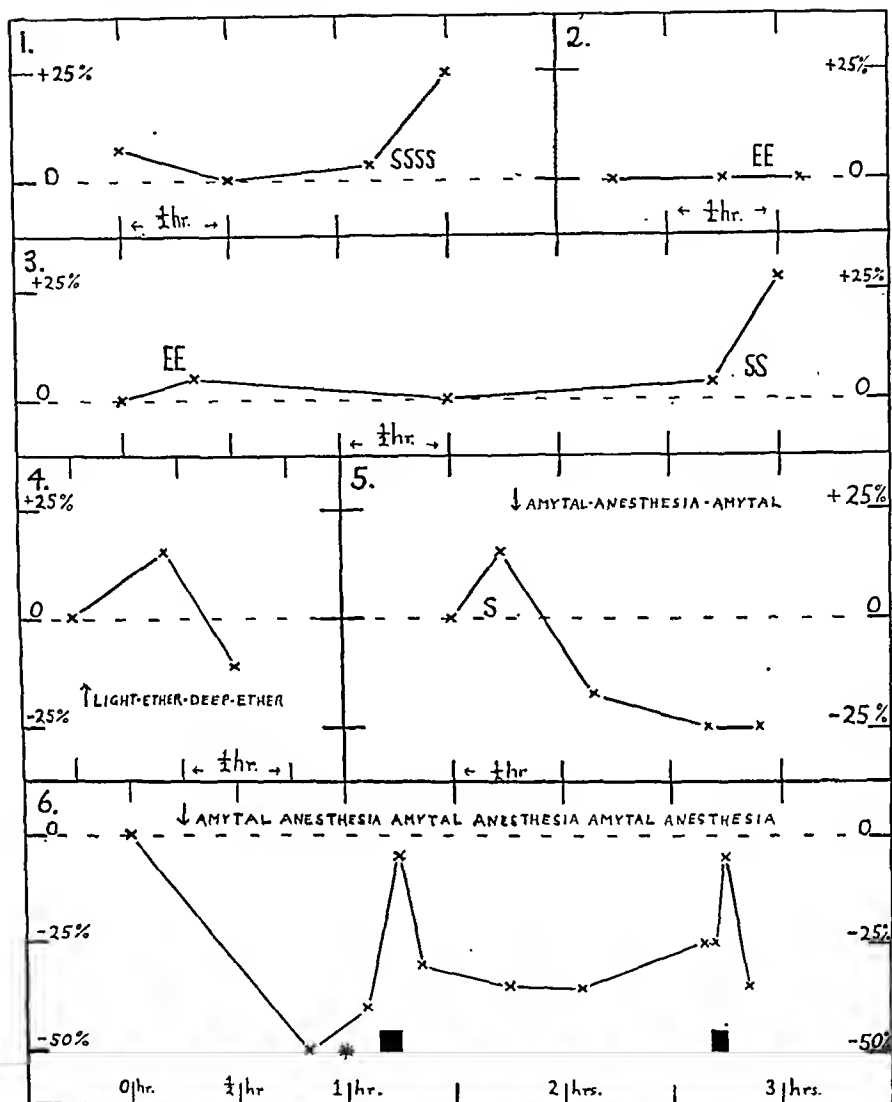
Effect of Excitement Without Muscular Work. Three experiments on 2 animals showed no significant immediate or delayed change in the white cell count following 10 minutes excitement. The small number of satisfactory observations was due to the difficulty in obtaining emotional reactions in the animals without accompanying muscular activity.

Effect of Ether Anesthesia. In 11 experiments on 6 animals, ether anesthesia for 15 minutes caused a significant rise in 7 cases. The lowest rise was 10.0%, the highest 113%; the average 35.28%. Two cases were insignificant. There was one drop of 28%. The effect of prolonged anesthesia was studied in 7 experiments on 4 animals. A complete experiment including initial and postanesthesia counts lasted from 1½ to 3¾ hours. The average time necessary to induce anesthesia was 12.5 minutes. There was an initial leukocyte rise in 6 out of 7 cases. Anesthesia was then continued for periods varying from 20 to 55 minutes. The total counts rose further in 3 cases, and dropped in 3 others. One case died from an overdose of ether. The number of minutes' exposure to ether had no apparent tendency to cause either a rise or a fall of the white blood cells, but the depth of anesthesia seemed to be a factor. Because of the initial rise, ether was discarded in our tests for the effects of passive exercise.

Effect of Amytal Anesthesia. In 13 experiments on 9 animals, sodium amytal in anesthetic doses caused a fall of the total white cell count in all cases. This generally occurred within 30 minutes and persisted for 4 to 5 hours. The smallest drop was 5%, the greatest 75%, the average 36.2%. Rises obtained after passive exercise under amytal were considered significant and due to the muscular work.

Effect of Passive Exercise Under Anesthesia. Of 9 observations on 4 animals, 7 showed definite elevation of leukocytes. These ranged from 11% to 50% in 3 to 10 minutes with an average rise of 29.2% in 8½ minutes. The changes in cell types were entirely mononuclear in 2 cases, mononuclear with some neutrophil rise in 4 cases, and a neutrophil rise in 1 case. There was one drop in the total count of 27%, and one insignificant rise. A poly- and a mononuclear decrease occurred in the 1 case of leukopenia. The nature of the insignificant rise was not determined. In this group a complete experiment lasted from 2 to 6 hours.

Exposure to 0° C. In 9 experiments, 7 animals were exposed to cold for 15 to 120 minutes. The total count rose in 2 and fell in 3



Graph I. Changes in total blood leukocyte counts under various experimental conditions.

Fig. 1.—After about an hour's quiet, the animal was made to struggle for 15 minutes. Fig. 2.—Excitement of a fast elevator ride failed to increase the total leukocyte count.

Fig. 3.—Same as Fig. 2, but the count increased when later muscular effort was added.

Fig. 4.—Ether administration was accompanied by a rise during light and a fall during deep anesthesia.

Fig. 5.—A moderate rise as a result of slight struggle was followed by a leukopenia as an injection of amytal began to take effect.

Fig. 6.—The low leukocyte count under amytal is modified by handling the animal in putting it on the machine. A brisk run increased the count, which fell again 5 minutes after cessation of exercise. A second similar run indicated that the rise was present after 3 but not 2 minutes of induced running.

S = Struggle

EE = Elevator excitement

↑ = Beginning of anesthesia

* = Animal put on machine

■ = Passive exercise

0 = Basal count when cat is resting quietly

cases. In the other 4 experiments the changes were insignificant. Cold affected the total count in a variable manner.

Discussion. Our results are in agreement with others in regard to the effect of muscular work. In the experimental animals, passive muscular work under anesthesia caused a rapid increase in white blood cells, which in a majority of the cases was due chiefly to mononuclear cells. The rise in the total count occurred within 5 minutes of onset of exercise, persisted throughout its duration and dropped rapidly toward normal following cessation of work.

Marked variations in the blood count of normal individuals after various forms of muscular work were noted as early as 1903 by Hawk. Since then others (Hasselbalch and Heyerdahl, 1908; Grawitz, 1910; Hochstetter, 1910; Ellermann and Erlandsen, 1911; Garry and Butler, 1929) have also observed a change in the number of leukocytes with a change in posture. They attribute the increase to circulatory shifts with liberation of leukocytes trapped in unused capillaries.

It seems probable that the main factor in the rapid production of leukocytosis following exercise is the dilatation of collapsed capillaries. With the muscles at rest there are vast numbers of inactive vessels holding on their walls many white blood cells. With activity these capillaries open, the cells are swept into the circulation and raise the total count.

The possibility of autonomic nervous control of leukocytosis and leukopenia has been suggested by Camus and Pagniez (1908), Mora, Amtman and Hoffman (1926) and Menkin (1928).

The effect of combined emotional and muscular stimulus does not differ appreciably in our experiments from that of muscular work alone, and we were unable to show any increase in white blood cell count from emotional stimulus in the absence of muscular work. We believe that the effects obtained by others and ascribed to emotion are due to a combination of motion and emotion, with major effects by motion. In a few of our cases the animals remained perfectly quiet and not under restraint, although sympathetic stimulus was evidenced by erection of the hair and dilatation of the pupils. No increase in leukocytes occurred. Our failure to obtain a leukocyte rise with excitement alone may be due to a limited circulatory adjustment in the absence of muscular response to the emotional stimulus.

We believe that during excitement with activity the circulation changes resulting in leukocytosis may be due to a reflex and not a generalized sympathetic discharge. The reflex would be induced by the need for blood in the active tissues (skeletal muscle). If a strong, generalized sympathetic discharge without accompanying muscular activity could be obtained, one might get a purely emotional leukocytosis. This is suggested by the results obtained with injections of adrenalin (Camus and Pagniez, 1908). The muscular activity factor will, however, be a difficult one to rule out.

The period of excitation during ether anesthesia in our animals was accompanied by a rise of the total white count. This rise can be explained by the excessive activity of the animals. The total count dropped during very deep anesthesia, but rose again during the recovery phase.

The leukopenia during amytal anesthesia makes the rises following passive exercise doubly significant in those cases.

The differences encountered in animals exposed to cold may also be explained by their relative activity. Our experiments were conducted in a small darkened refrigerator in which the animals generally remained quiet. Furthermore, exposure to cold while the animal was under ether anesthesia caused a leukopenia. In experiments by Zwemer and Lyons (1928), cats were subjected to cold in a large well-lighted refrigerating room, in which considerable activity was possible. An increase in total counts occurred in their cases, except in those animals that had had their sympathetic nervous system removed.

Other types of physiologic leukocytosis have been described (Rous 1908, Scheider and Havens 1915, Becher 1918). Although some of them are undoubtedly contributory factors, their speed of reaction is probably too slow to account for the rapid rises encountered in the experiments reported in this paper.

The rhythmic basal changes in normal human subjects (Japha, 1900; Galambos, 1912; Sabin, Cunningham, Doan and Kindwall, 1925) also differ in their time relationships from our experimental results.

Summary. 1. Emotional stimulus with muscular activity was followed by a leukocytosis. This was generally mononuclear in type.

2. Emotional stimulus alone in our few cases effected no significant variation of total white count.

3. Passive work under anesthesia raised the total white cell count, the rise being similar to that induced by excitement plus activity.

4. The rapid increase following muscular work is probably due to a dilatation of unused muscle capillaries, the entrapped leukocytes being swept into the general circulation.

5. Sodium amytal (intramuscularly in anesthetic doses) caused a constant leukopenia.

6. Ether anesthesia was characterized by an initial leukocytosis, the elevation being evidenced by all cell types. Deep anesthesia was accompanied by a drop in the total count. These effects may be correlated with the initial hyperactivity and subsequent relaxation of the animal.

7. Exposure to cold (0° C.) produced no constant change in the total white count.

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THE SCHILLING COUNT IN 59 CASES OF CHRONIC ARTHRITIS WITH A CORRELATED SEDIMENTATION RATE IN 30 CASES.

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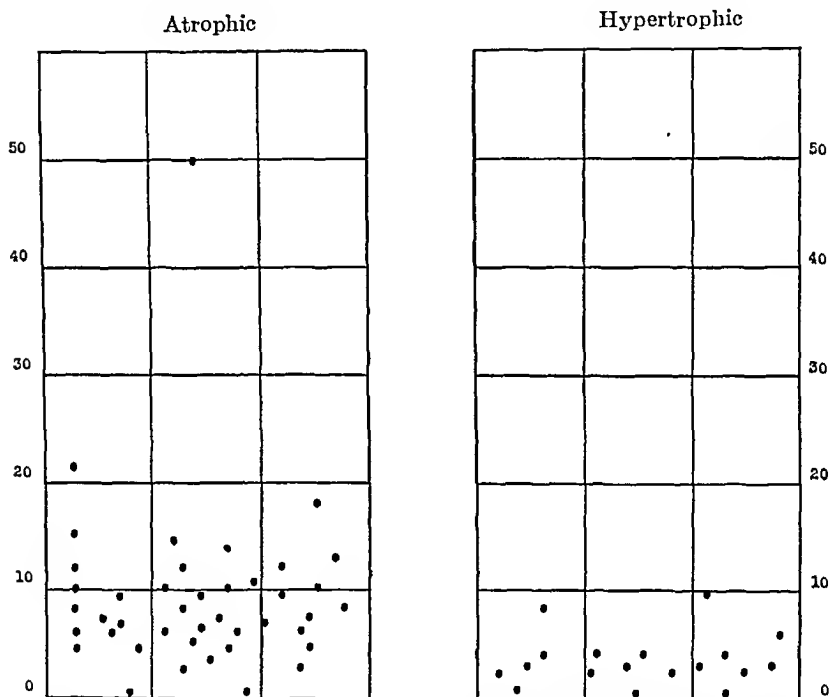
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THE system of differentiation of the white blood cell count as developed by Schilling in 1911 has proved to be of much value in the diagnosis, prognosis and treatment of disease. The voluminous literature on the subject certifies this fact. Crocker and Valentine,¹ after a careful and very interesting analysis of 6000 Schilling hemograms, state that the method is most practical and scientific. And yet a careful study of the literature on chronic arthritis reveals very little study as regards the Schilling count in this chronic disease. Also there have been extensive studies of the sedimentation rate in joint disease, but, as far as I know, no one has attempted a correlated study of the younger neutrophils and the sedimentation

rate. The opinion cited by Oppel² and his co-workers, that an isolated observation of the sedimentation rate is of little value in differentiating various forms of arthritis, is to be seriously considered.

The author has studied 59 cases of chronic arthritis with particular emphasis of the Schilling differential as a means of differentiating the two main types of chronic arthritis. He also has correlated this study with sedimentation determinations by the method described by Rourke and Ernstone³ in 30 cases. That there is a definite correlation between the Schilling count and the sedimentation rate is well demonstrated by a study of Charts I and II. In atrophic

CHART I.—THE SCHILLING COUNT IN 59 CASES OF CHRONIC ARTHRITIS.



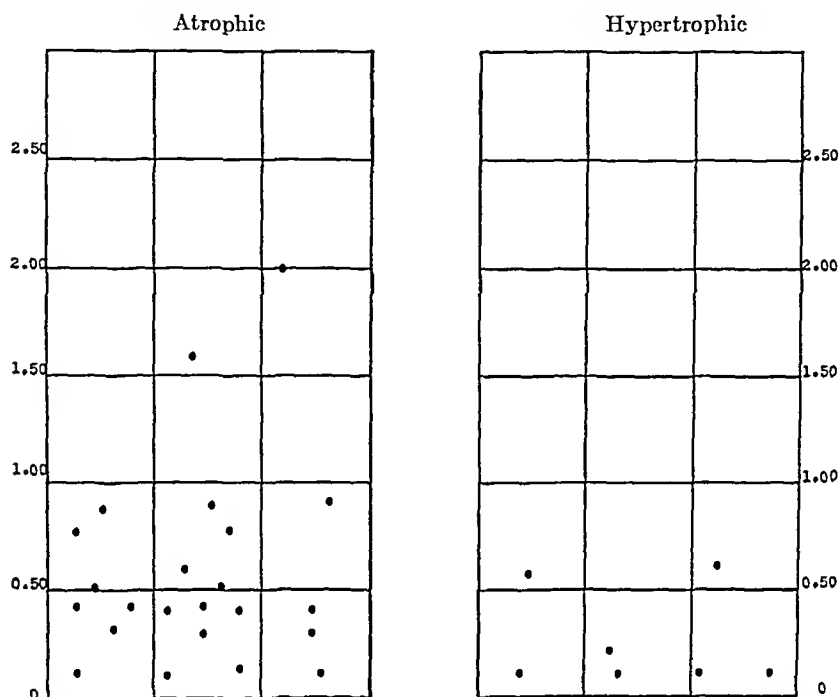
Note that most cases of atrophic arthritis are above 4%, whereas most cases of hypertrophic arthritis are 4% or below. (Scale is in per cent of younger neutrophils—myelocytes, juveniles and stabnuclears combined.)

arthritis the percentage of the younger neutrophils is increased over the normal in most cases, whereas, in hypertrophic arthritis these cells are usually not increased. The sedimentation rate, in general, follows the same general trend. However, it is evident that many of the cases of atrophic arthritis show an upper level of normal sedimentation rate (normal index is 0.8 to 0.35).

Table 1 includes 42 cases of atrophic arthritis. In this group, the Schilling was shifted to the left in 33 cases (78%). Four of the 9 cases in which the Schilling was not shifted to the left showed the upper limit of the normal younger polys. That the stage of the

disease in which the Schilling count is done is important is demonstrated by G. D. During the acute phase of the arthritis there were 12% of the younger neutrophils present in the blood smear, whereas, during the resting stage in the same case there were only 3% of these cells present.

CHART II.—THE SEDIMENTATION RATE IN 30 CASES OF CHRONIC ARTHRITIS.



Note that most cases of atrophic arthritis are above 0.35, whereas, most cases of hypertrophic arthritis are below 0.35. (Scale in mm. per minute.)

Table 2 includes 17 cases of hypertrophic arthritis. In this group the Schilling was shifted to the left on only 3 cases (17%). Of these 3 cases the highest percentage of cells younger than the stabnuclear stage was 2% juveniles, whereas, in the atrophic group we find 12% juveniles in 1 case and in another we even find 2% myelocytes.

In the correlated study there is agreement of the Schilling count and the sedimentation rate in 22 instances and disagreement in 8 cases. By "agreement" the author means that both the sedimentation rate is diminished in time and the Schilling is shifted to the left. The shifting of the Schilling to the left and a normal sedimentation rate, or a normal Schilling differential with a sedimentation rate which is decreased in time, is called "disagreement" in this paper. In 29 instances the Schilling count substantiates the clinical diagnosis and fails to do so in only 1 case. The sedimentation rate substantiates the clinical diagnosis in 22 cases and does not in 8 instances. From this preliminary correlated study it would seem that

the Schilling count is more valuable than the sedimentation rate in differentiating the two main types of chronic arthritis.

TABLE 1.—SCHILLING DIFFERENTIALS IN 59 CASES OF CHRONIC ARTHRITIS WITH A CORRELATED SEDIMENTATION RATE IN 30 CASES.
(ATROPHIC ARTHRITIS.)

	My. %	Juv. %	Stabs. %	Segs. %	Lyms. %	Monos. %	Eos. %	Bas. %	Sed. time.
L. McN.	12	38	32	14	3			
I. C.	2	3	16	40	30	5	2	2	0.80
M. M.	3	15	45	30	3	4	..	0.70
M. C.	15	44	34	5	..	2	0.59
S. Z.	14	54	27	5	0.80
H. H.	1	3	9	39	41	3	4	..	2.00
E. S.	2	11	55	26	2	4	..	1.55
G. D. (acute stage)	1	2	9	41	40	..	6	1	
T. C.	2	10	47	39	..	2	..	0.43
C. P.	1	11	72	16				
G. H.	11	27	57	3	2		
A. G.	3	7	69	15	4	2		
C. G.	1	9	50	37	1	2	..	0.80
B. M.	1	9	58	26	3	3		
R. M.	10	63	23	3	0.10
E. L.	9	57	25	6	3		
R. H.	9	62	24	5	0.20
M. R.	9	69	20	1	1		
G. B.	2	6	67	21	..	4	..	0.38
M. B.	8	65	22	5			
C. M., combined (atrophic pre- dominating)	8	46	39	5	2	..	0.15
A. M.	2	5	33	50	..	2	1	
A. V.	7	72	18	3			
M. DeL.	7	49	41	3	0.50
F. H., combined (atrophic pre- dominating)	7	42	47	2	2	..	0.10
H. A.	7	53	22	5	3	..	0.75
V. M.	6	78	26				
J. F.	6	71	18	1	4	..	0.50
L. DeM.	6	68	23	..	3	..	0.38
H. W.	6	42	48	4	0.30
C. F.	6	59	31	2	2	..	0.40
A. W.	6	68	24	2	0.39
J. M.	5	75	17	1	2		
L. T.	4	67	25	3	1		
A. N.	4	60	33	1	2	..	0.35
E. W.	4	71	16	6	3		
B. R.	4	79	12	5			
G. D. (resting stage)	3	67	25	1	4		
M. K.	3	52	39	5	1		
D. K.	2	35	60	2	1	..	0.40
H. P.	2	64	19	10	3	1	
G. H.	68	29	3			
C. B.	50	50				

Another interesting observation from the correlated study is that in all instances in which the stabnuclear count is above 10% and in

all cases in which we find younger neutrophils than the stab state, the sedimentation rate is more rapid than normal. In all such cases the author has always encountered the atrophic type of arthritis. This fact is well demonstrated by a study of the tables. In only 1 case of atrophic arthritis (A. N.) do we find both a normal Schilling differential and a normal sedimentation rate and in this case both values are the upper limit of normal. Furthermore, this was a "burnt out" case of atrophic arthritis.

TABLE 2.—SCHILLING DIFFERENTIALS IN 59 CASES OF CHRONIC ARTHRITIS WITH A CORRELATED SEDIMENTATION RATE IN 30 CASES.
(HYPERTROPHIC ARTHRITIS.)

	My. %	Juv. %	Stabs. %	Segs. %	Lymbs. %	Monos. %	Eos. %	Bas %.	Sed. time.
J. Q. (Mixed arthritis, hypertrophic pre- dominating)	..	2	7	52	34	2	3		
W. B. (acute knee joint)	..	1	7	38	56	3	5		
L. N.	6	70	22	..	2		
N. W.	4	64	22	8	2	..	0.65
C. B.	4	68	27	1	0.20
A. F.	4	42	44	2	8	..	0.21
G. R.	3	61	33	1	2	..	0.60
C. S.	3	64	29	2	2	..	0.15
R. B.	3	45	37	7	8		
C. G.	3	73	24				
S. S.	2	68	25	..	2	1	0.27
F. W.	2	45	47	2	3	..	0.23
E. B.	2	56	40	..	2	..	0.31
G. S.	2	66	30	..	2		
J. M.	68	36	6			
C. A.	68	26	6			
N. P.	68	26	5	1		

From this preliminary study it would seem that the Schilling count is of value in differentiating the two main types of chronic arthritis. The sedimentation rate as described by Rourke and Ernste, together with a Schilling differential, increase the accuracy with which this differential study may be made. Only in 4.7% of the total cases of atrophic arthritis did the author obtain both a normal Schilling count and a normal sedimentation rate. The practical application of this study in the treatment of chronic arthritis will be discussed in a future article.

Summary. 1. Schilling studies in 59 cases of chronic arthritis are presented.

2. Thirty cases of chronic arthritis with both Schilling differentials and sedimentation rates are discussed.

3. The Schilling count is of value in differentiating atrophic from hypertrophic arthritis.

4. Correlated studies of the Schilling count and the sedimentation rate seem to increase the accuracy with which this differential study can be made.

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INCIDENCE OF INFECTION WITH INTESTINAL PROTOZOA IN MINNESOTA.

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CRAIG¹ has estimated that between 5% and 10% of the population of the United States are carriers of *Endamoeba histolytica*. It is well known that a higher percentage of infestation occurs in warm climates and under crowded living conditions.^{2,3} Kofoid and Swezy⁴ found *E. histolytica* present in the stools of 67% of 91 soldiers examined who had recently returned from overseas duty in the World War. Meleney, Bishop and Leathers⁵ reported 11.4% infestation in the rural districts of Tennessee. In a survey carried out by Andrews and Paulson⁶ in 1931, however, *E. histolytica* was found in only 0.3% of 312 individuals who were living under normal home conditions in Baltimore. And more recently Hinshaw and Showers,⁷ working in Philadelphia, found 1.1% of 368 unselected hospital patients positive when examined. Riley,⁸ in 1929, examined a selected group of approximately 500 ex-service men in Minnesota and found 1.4% infected with *E. histolytica*. He concluded "that *E. histolytica* is distinctly less common in the north central states than might be inferred from current statistics."

Dobell⁹ has estimated that about one-third of the actual *E. histolytica* infections will be discovered by a single examination. Carter and coworkers¹⁰ found on the first examination 33.4% of the total number of infections with *E. histolytica* which were found on 6 examinations. Kessel and Svensson,¹¹ in Peking, report the following percentages of the total infections which were found on the first examination in a series of 6 examinations: *E. histolytica*, 44%; *E. coli*, 47%; *E. nana*, 47%; *Iodamoeba*, 30%; *Chilomastix*, 29%; *Giardia*, 42%.

In examining stools for intestinal protozoa, Magath and Ward¹² prefer the study of a fresh preparation of liquid stools obtained

after a saline purge to any other single method. Spector,¹³ in 1932, concluded "in the detection of *E. histolytica* infections, cultural methods are probably superior to direct fecal examination."

The present investigation was carried out to ascertain the presence of *E. histolytica* carriers among the healthy working food handlers of a large railway system, a single* examination was made, except in positive cases, when a second specimen was included. The following results are the actual findings without calculations as to the probable percentage of infection; 146 apparently normal working employees were examined. None of this number gave a history of past infection with *E. histolytica*.

Material and Methods. The examinations were made upon fresh stools passed at the laboratory after the administration of a saline cathartic. The examination consisted of:

1. Immediate examination of a fresh preparation using a warm stage to guard against loss of temperature.

2. Examination of a portion of the stool emulsified in 1% I in 2% KI, as recommended by Craig.

3. Culture of the stool on Cleveland's¹⁴ media. This was incubated 24 hours at 37° C., and a portion searched on the warm stage for motile forms.

Results. In the detection of *E. histolytica* there was complete agreement between the cultural and direct examination methods. That is, none of the stool cultures showed the presence of *E. histolytica* except those in which *E. histolytica* had been found in the fresh stool by direct examination.

The per cent infestation with other protozoan parasites reported is compiled from the findings of the fresh preparation and iodine stain methods. The following table shows the incidence of infestation with protozoan intestinal parasites in a series of 146 apparently normal working individuals.

TABLE 1.—INCIDENCE OF INTESTINAL PROTOZOA.

Organisms.	No. of cases.	Per cent.
<i>E. histolytica</i> alone	0	0
<i>E. histolytica</i> and <i>B. hominis</i>	1	0.68 +
<i>E. histolytica</i> and <i>B. hominis</i> and <i>E. nana</i>	1	0.68 +
<i>E. coli</i> alone	1	0.68 +
<i>E. coli</i> and <i>B. hominis</i>	6	4.11
<i>E. coli</i> and <i>B. hominis</i> and <i>Iodamoeba bütschlii</i>	1	0.68 +
<i>Endolimax nana</i> alone	3	2.0
<i>Endolimax nana</i> and <i>B. hominis</i>	9	6.16
<i>Endolimax nana</i> and <i>I. bütschlii</i>	1	0.68 +
<i>Endolimax nana</i> and <i>B. hominis</i> and <i>C. mesnili</i>	1	0.68 +
<i>Iodamoeba bütschlii</i> alone	1	0.68 +
<i>Iodamoeba bütschlii</i> and <i>B. hominis</i>	1	0.68 +
<i>Giardia intestinales</i> alone	1	0.68 +
<i>Giardia intestinales</i> and <i>B. hominis</i>	1	0.68 +
<i>Chilomastix mesnili</i> alone	0	0
<i>Chilomastix mesnili</i> and <i>B. hominis</i>	2	1.37
<i>Trichomonas hominis</i> alone	1	0.68
<i>Trichomonas hominis</i> and <i>B. hominis</i>	1	0.68
<i>Blastocystis hominis</i> alone	54	37.0

* Before additional examinations could be made the order authorizing the survey was rescinded.

TABLE 2.—TOTAL INCIDENCE.

Organisms.	No. of cases.	Per cent.
<i>E. histolytica</i>	2	1.37
<i>E. coli</i>	8	5.50
<i>E. nana</i>	15	10.27
<i>I. bütschlii</i>	4	2.74
<i>G. intestinales</i>	2	1.37
<i>C. mesnili</i>	3	2.05
<i>T. hominis</i>	2	1.37
<i>B. hominis</i>	78	53.42
Negative	60	41.10

Discussion. Of the 146 individuals whose stools were examined, the stools of 24.67% were found to contain at least one of the intestinal parasites other than *B. hominis*. Since the significance of *B. hominis* is at present somewhat undetermined it has been included in this study. *Blastocystis hominis* was present in the stools of 37% of the individuals, unaccompanied by any other parasite. Forty-one per cent of the stools were found to contain no protozoan parasite.

Since this investigation embraces an unselected group of working and apparently healthy individuals, it serves to show that a small percentage of the normal population in the north central United States are carriers of *E. histolytica*. However, this percentage of carriers is not as great as the 5 to 10% which Craig has estimated for the entire United States. Nevertheless, with the increasing facility of travel, the low percentage of 1.37 reported might well reach a higher level within a few years.

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THE HETEROPHIL ANTIBODY TEST IN LEUKEMIA AND LEUKEMOID CONDITIONS.*

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THIS study is an attempt to confirm the original observation of Bernstein (1934) that in leukemia the heterophil antibody titre is uniformly at a low level, and to investigate heterophil antibody formation in leukemia and certain leukemoid conditions before and after the parenteral administration of horse serum. A heterophil antibody is an antibody group possessing the capacity to react with antigens, different from and phylogenetically unrelated to the specific antigen instrumental in producing the antibody response.

Method. The method used in this study is similar to that employed by Davidsohn (1929, 1930), Paul and Bunnell (1932), Bunnell (1933), and Bernstein (1934). The following materials are employed: Serum of the patient, a 2% suspension of washed sheep red cells, and physiologic saline solution. The serum is inactivated at 56° C. for 15 minutes, and diluted in physiologic saline in a series ranging from undiluted serum to a dilution of 1 to 16, or as far as is indicated. To each tube containing 0.5 cc. of diluted serum, 0.5 cc. of a 2% solution of washed sheep red cells is added and finally the addition of 1 cc. of physiologic saline brings the total volume to 2 cc. The tubes are shaken, placed in a water bath at 37° C. for 1 hour and kept overnight in the ice box. The next morning the tubes are inverted 3 times and the degree of sheep cell agglutination is recorded as follows:

+++ single mass of cells; ++ large flakes; + fine flakes; 0 no agglutination.

To facilitate comparison with the results of previous workers, the serum dilutions are expressed in terms of the proportion of serum to saline present in the original 0.5 cc. added and *not* with reference to final serum dilution, *i. e.*, "undiluted" is actually 1 to 4, a 1 to 1 dilution is 1 to 8, and so forth.

* Presented before Section on General Medicine, College of Physicians, Philadelphia, December 18, 1934.

Previous workers have found, in normal individuals and in patients suffering from a variety of diseases with the exception of infectious mononucleosis and serum sickness, that sheep cell agglutinins may be present up to a serum dilution of 1 to 16. Bernstein (1934) for purposes of convenience, designated the range of serum dilutions below 1 to 4 as Zone 1, the interval between 1 to 4 and 1 to 16 as Zone 2, and the distribution above 1 to 16 as Zone 3. Bernstein (1934) found that in over 300 cases other than serum sickness or infectious mononucleosis, 30% fell in Zone 1 and 70% in Zone 2. Similarly Bunnell (1933) in over 1600 cases found that 40% fell in Zone 1 and 60% fell in Zone 2. Stuart *et al.* (1934) found that in 300 cases 26% fell in Zone 1 and 74% in Zone 2. In a series of 100 hospital cases unselected except to exclude serum sickness, infectious mononucleosis and leukemia, we found that 36% fell in Zone 1 and 64% fell in Zone 2, and no case fell in Zone 3. Thus it seems safe to assume that normal individuals and those suffering from a variety of diseases other than serum sickness and infectious mononucleosis all exhibit a heterophil antibody titre of less than Zone 3 magnitude. Furthermore, of this group at least 60% fall in Zone 2.

TABLE 1.—LOW HETEROPHIL ANTIBODY RANGE IN LEUKEMIA.

Case No.	Diagnosis.	Zone 1.			Zone 2.	White blood cells, range.	
		Undil.	1 to 1.	1 to 2.	1 to 4.		
1	Acute lymphatic leukemia	+	+	—	—	22,000	
2	Chronic lymphatic leukemia	—	—	—	—	53,800	22,000
3	" " "	—	—	—	—	98,200	11,000
4	" " "	—	—	—	—	38,000	27,000
5	" " "	—	—	—	—	21,800	106,000
6	" " "	+	—	—	—	4,200	8,600
7	Acute myelogenous leukemia	—	—	—	—	14,000	
8	" " "	+++	+++	+++	++	42,000	
9	Chronic " "	—	—	—	—	420,000	9,000
10	" " "	+	—	—	—	9,200	22,400
11	" " "	+	—	—	—	188,000	64,000
12	" " "	—	—	—	—	20,000	137,000
13	" " "	++	+	—	—	14,000	68,000
14	" " "	+	—	—	—	90,000	11,200
15	" " "	++	+	—	—	20,000	320,000
16	" " "	—	—	—	—	82,000	
17	Subleukemic myel. leukemia	+	—	—	—	2,600	9,400

Seventeen cases of leukemia were studied—1 of acute lymphatic leukemia, 5 of chronic lymphatic leukemia, 9 of chronic myelogenous leukemia and 2 of acute myelogenous leukemia. In all these cases the heterophil antibody titre fell in Zone 1 and in no instance could heterophil antibody be demonstrated above a serum dilution of 1 to 1—except in a single case of acute myelogenous leukemia who had received 28 transfusions. These results confirm the previous work

of Bernstein (1934), who reported that 20 of 21 cases of leukemia had a heterophil titre that fell in Zone 1.

This finding of a low heterophil antibody content in the serum of patients with leukemia was not influenced by the level of the leukocyte count, or by the predominating cell present, and was obtained irrespective of whether or not the patient had received radiation therapy. It was also noted that a tremendous shift of the blood picture from that of florid leukemia to a strictly aleukemic phase did not influence this constantly low heterophil antibody level.

We also found in a study of 5 cases of proven lymphosarcoma and 3 cases of Hodgkin's disease, a constantly low titre of heterophil antibody, all falling in Zone 1.

We conclude from these observations that with heterophil antibodies distributed in Zone 2 or Zone 3, one may with some assurance rule out leukemia. However, if the heterophil antibody titre falls in Zone 1, the patient may or may not have leukemia. The heterophil antibody test up to this point is therefore of value only in establishing *negative* evidence concerning the diagnosis of leukemia.

Previous workers have shown that specific antibody formation in leukemia is disturbed. Moreschi (1914) was able to demonstrate little or no specific agglutinin formation after the injection of typhoid vaccine in 6 cases of chronic myelogenous leukemia and 2 cases of chronic lymphatic leukemia. Rotky (1914) using a harmless vibrio cultivated from water was able to demonstrate specific agglutinin formation in 8 control cases, but could not demonstrate any agglutinin formation in 2 cases of leukemia (1 chronic myelogenous and the other chronic lymphatic).

Davidsohn (1929) first reported that following the administration of horse serum there was an increase in *heterophil* antibody titre. He later reported (1933) a series of heterophil titres in cases receiving immune sera for therapeutic purposes. The average titre for the control group was a serum dilution of 1 to 6, the average titre for the group receiving serum but in whom serum sickness did not develop was a serum dilution of 1 to 18 and in the group developing serum sickness, the average heterophil titre was a serum dilution of 1 to 63. Bernstein (1934) found an increase in the heterophil antibody titre in 11 cases receiving various immune sera. In our study the heterophil antibody titre in 14 non-leukemic cases which had received various immune sera was found to be in the serum dilution range of Zone 3, thus confirming the work of these investigators.

Bernstein (1934) injected horse serum intravenously in a case of chronic lymphatic leukemia and could demonstrate no increase in heterophil antibody content of the serum. A second case of probable leukosarcoma showed a minimal rise in heterophil antibody titre after the parenteral administration of horse serum. Neither of these cases developed evidence of a serum reaction.

This finding in leukemics contrasts sharply with Davidsohn's (1933) demonstration of a constant increase in heterophil antibody titre after parenteral administration of horse serum in non-leukemics regardless of whether or not serum sickness occurred. This suggests the possibility that in leukemic individuals the mechanism of heterophil antibody formation may be inhibited or deficient just as the mechanism of specific antibody formation is deficient.

The evidence thus far suggests that normal individuals and those suffering from a variety of disorders show a rise in heterophil antibody titre from Zone 1 (40% of total group) or Zone 2 (60% of total group) to Zone 3 when given horse serum parenterally, whereas the few leukemics previously tested (all in Zone 1) show no significant rise of heterophil antibody titre after the administration of horse serum. This difference in response to horse serum might seem to offer a positive means of establishing the diagnosis of leukemia.

TABLE 2.—HETEROPHIL ANTIBODIES IN LEUKEMICS BEFORE AND AFTER RECEIVING HORSE SERUM.

Case.	Clinical diagnosis.	Biopsy.	Type.	Undil.	1 to 1.	1 to 2.	1 to 4.
S.	Chr. lymph. leuk.	Atypical lymph. leuk.	O	—	—	—	—
D.	Chr. lymph. leuk.		O	— +	— +	—	—
D.	Chr. lymph. leuk.	Chr. lymph. leuk.	A	—	—	—	—
C.	Chr. lymph. leuk.		A	— +	— +	—	—
B.	Chr. subleuk. lymph. leuk.	Lymph. leuk.		— ++	— +	—	—
H.	Chr. myel. leuk.		B	— +++	— ++	— +	—
M.	Chr. myel. leuk.		B	— +++	— +++	— +++	— 1 to 64 +
M.	Chr. myel. leuk.		O	— +++	— +++	— +++	— 1 to 512 +
F.	Chr. aleuk. leuk. vs. lymphosarc.	Chr. aleuk. leuk. vs. lymphosarcoma	A	— +	—	—	—
M.	Aleuk. leuk. vs. lymphosarc.	Lymphosarcomatous type of hyperplasia		— ++	— +	—	—
P.	Hodgkin's dis. vs. aleuk. leuk.	Atypical Hodgkin's dis.		— +++	— ++	— +	—
L.	Subleuk. lymph. leuk.	Chr. inflammation		— +++	— +++	— +++	— 1 to 32 +
G.	Monocytic leuk.?		O	— +++	— +++	— +++	— 1 to 64 +

The upper titration represents the heterophil antibody titre present before the administration of horse serum. The lower titration represents the highest titre after horse serum injection.

This possibility was investigated in 8 cases of known leukemia and 5 in which the differential diagnosis was in doubt. After

obtaining at least 2 determinations of heterophil titre on separate days, the patient received an intradermal injection of 0.05 cc. of normal horse serum. In the absence of a positive reaction, 5 cc. of horse serum were injected intramuscularly into the buttock. The next day 10 cc. of the serum were injected into the opposite buttock. Blood was withdrawn at frequent intervals following the serum injections and the heterophil titre determined. In several cases the heterophil titre was determined for periods of 6 weeks after serum injection.

This leukemic group was composed of 5 cases of chronic lymphatic leukemia and 3 cases of chronic myelogenous leukemia. We also tested 2 cases in which the diagnosis by biopsy rested between aleukemic leukemia or lymphosarcoma, 1 diagnosed by biopsy as atypical Hodgkin's disease, 1 with generalized lymph node enlargement, a white count of 13,600 and a differential count with 73% lymphocytes diagnosed by biopsy as "hyperplasia of chronic inflammation," and 1 in whom a monocytosis associated with an enlarged spleen raised the possibility of monocytic leukemia.

The 5 cases of chronic lymphatic leukemia had no significant rise in heterophil antibody titre after horse serum injection. In no instance did the heterophil titre shift beyond Zone 1.

The 3 cases of chronic myelogenous leukemia, however, had a *marked* change in heterophil antibody titre after the administration of horse serum. In 1 case there was a rise from no agglutination in "undiluted" serum to definite agglutination in a dilution of 1 to 2. In the other 2 cases the agglutinin titre rose from the range of Zone 1 to agglutination in a serum dilution of 1 to 64 in one, and to agglutination in a serum dilution of 1 to 512 in the other. In the last case the agglutinin titre started to rise 5 days after serum injection and 2 days later the patient had a moderately severe attack of serum sickness. None of the other cases of leukemia developed serum sickness.

In the 2 cases in which the diagnosis by biopsy rested between aleukemic leukemia and lymphosarcoma and in the case diagnosed as atypical Hodgkin's disease by biopsy, there was no shift in the agglutinin titre out of the range of Zone 1 after serum administration.

The case of generalized adenopathy with lymphocytosis diagnosed by biopsy as "hyperplasia of chronic inflammation" and the case in which monocytic leukemia was suspected, each exhibited a shift in heterophil antibody from Zone 1 to Zone 3. Both of these individuals recovered completely and follow-up examinations show them to be in good health.

It is evident that in our small series of cases of chronic lymphatic leukemia administration of normal horse serum does not produce an increase in heterophil antibody. On the other hand, the parenteral administration of normal horse serum in the cases of chronic

myelogenous leukemia elicits an increase in heterophil antibody in no wise differing from that produced in non-leukemic individuals. Thus it is apparent that no difference between the non-leukemic and chronic myelogenous leukemia cases can be established on the basis of this procedure.

Our findings indicate that the response of heterophil antibody formation following the parenteral administration of horse serum may possibly be of value in separating cases of lymphatic leukemia, aleukemic lymphatic leukemia, lymphosarcoma, and Hodgkin's disease on the one hand, from normals and from other diseases on the other hand. It is of no value in differentiating between lymphatic leukemia, lymphosarcoma and Hodgkin's disease, which, as far as this evidence goes, seem to be serologically related. It is furthermore obvious that myelogenous leukemia falls within the normal range of response to serum administration and thus diverges sharply, and to us unexpectedly, from the lymphatic leukemia group.

It is of interest to note the results of serum administration in a case of general lymph adenopathy with a white count of 13,600 and a lymphocyte percentage of 73. The clinical diagnosis was chronic lymphatic leukemia in the subleukemic stage. The original heterophil antibody titre fell in Zone 1 and was compatible with the diagnosis of leukemia. However, after serum administration, the heterophil antibody titre rose into the range of Zone 3. This led us to question the diagnosis of leukemia. A subsequent lymph node biopsy revealed "hyperplasia of chronic inflammation" and substantiated the inference drawn on the basis of the rise in heterophil antibody titre, that this case was not lymphatic leukemia. Follow-up study of this case indicates the correctness of this position in as much as this man is perfectly well.

A heterogenous group of cases was studied with the following findings: Two cases with tuberculous adenitis fell in Zone 2; 5 acute non-specific adenitis cases were distributed in Zones 1 and 2; 1 of secondary lues with generalized adenopathy fell in Zone 1; 5 of polycythemia vera were distributed in Zones 1 and 2; 4 of typhoid fever all still febrile fell in Zone 2; 3 of aplastic anemia fell in Zones 1 and 2; 3 of purpura hemorrhagica (thrombocytopenic) fell in Zones 1 and 2 and single cases of Felty's syndrome, primary pernicious anemia, and pneumonia fell in Zone 1. In sharp contrast to the findings in this heterogenous group, we have found in 10 cases of acute infectious mononucleosis a high titre of heterophil antibody (all in Zone 3). The heterophil antibody titre reached Zone 3 within a few days of the onset in typical cases, and roughly parallels the abnormal lymphocytosis which, however, may be present after the heterophil antibody titre has returned to normal levels. We have found a Zone 3 titre, however, 6 weeks after onset in 1 case and 12 weeks after onset in another. In 3 other cases, after 2 years, 8 months, and 12 weeks respectively, we found that the heterophil antibody titre was present in the normal range.

Conclusions. 1. The heterophil antibody titre in the sera of 16 cases of leukemia was found to be uniformly and repeatedly at a low level (Zone 1) regardless of the stage and type of the disease. One case of acute myelogenous leukemia was found to be in Zone 2. This case, however, had received 28 blood transfusions. This constant finding may be of value in ruling out the diagnosis of leukemia in any case in which a high heterophil antibody titre is found.

2. A low or normal titre of heterophil antibody was found also in 3 cases of Hodgkin's disease, 5 of lymphosarcoma, 5 of polycythemia vera, 4 of agranulocytic angina, and a number of miscellaneous cases including typhoid fever, simple adenitis, syphilis, tuberculosis, anemia, etc.

3. A high titre (Zone 3) was found in serum sickness and acute infectious mononucleosis, thus confirming the reports of Paul, Bunnell, Davidsohn and others.

4. The parenteral administration of horse serum did not produce a rise in the heterophil antibody titre in 5 cases of chronic lymphatic leukemia. This finding is in accord with previous evidence.

5. A similar failure of increase of heterophil antibody titre following horse serum injections was found in 1 case of "atypical" Hodgkin's disease and 2 of lymphosarcoma, suggesting the possibility of a biologic relationship of these conditions to lymphatic leukemia.

6. The parenteral administration of horse serum in 3 cases of chronic myelogenous leukemia produced a marked rise in heterophil antibody titre similar to that occurring in non-leukemic individuals. This finding is not in accord with previous evidence, and suggests the possibility of a real biologic difference between myelogenous leukemia on the one hand, and the lymphatic group on the other hand.

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PERNICIOUS ANEMIA AND MALIGNANT NEUTROPENIA: A CASE REPORT.

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THE occurrence of malignant neutropenia (agranulocytosis) as a terminal event in a case of pernicious anemia which was receiving active and adequate treatment seems worth reporting.

Case Report. Mrs. J. S. (No. 18073), American, was seen at her home in consultation on October 22, 1933. Her family, past and marital history were unimportant. She had passed the menopause in the late forties and had had no bleeding or discharge since. Her present illness began indefinitely in the summer or early fall of 1930 with weakness, vague indigestion and intermittent soreness of the tongue. In the early summer of 1933 there was a marked increase in these symptoms and about August she developed numbness and tingling in her hands and feet which gradually spread until at the time she was seen it involved the whole body below the neck. With the development of this numbness she became progressively more awkward until finally she could neither walk, feed nor care for herself nor even button her night dress. There was no involvement of the organic reflexes. For 6 weeks she had been bedfast, her appetite had been very poor and she had had frequent, irregular spells of nausea, vomiting and diarrhea. There has been a moderate though indeterminate loss in weight.

Examination showed a slim, thin, extremely pale, alert woman in the mid-sixties, apparently seriously and chronically ill. The pallor, however, was distinctly yellowish and the conjunctiva were subicteric. Her tongue was smooth and without papillæ and presented two or three hyperemic areas which were sore and tender. Her pupils reacted normally but there was complete absence of all the superficial and deep reflexes and bilateral positive Babinski signs. There was marked disturbance of coördination, sense of position and deep sensation in all the extremities, more marked in the lower. She could not recognize ordinary objects by the sense of touch. Pain sensation was moderately diminished and delayed. The remainder of the examination, including pelvic and rectal, was normal. Examination of the blood revealed hemoglobin, 20 to 25% (Tallqvist); erythrocytes, 1,220,000, and leukocytes, 5000. The stained preparations showed the changes characteristic of a high-grade macrocytic anemia. The differential count was unfortunately lost, but there were about 70% neutrophils, many of which were the multilobular type characteristic of the old forms seen in pernicious anemia.

She was placed upon the anemic diet of Minot and Murphy, given 15 capsules of "Extralin-Lilly" daily, dilute hydrochloric acid and a 3 cc. ampule of "Lederle's liver extract" intramuscularly twice a week. There was a striking response. By the early part of November her hemoglobin was 65% (Newcomer); red cells, 2,650,000; white cells, 5500; with neutrophils 71%. There were still marked changes in the morphology of the red cells with a tendency to macrocytosis.

When next seen, November 24, she was much stronger, could feed and care for herself and button her gown, but could not walk because her legs "wouldn't track." The numbness had receded to the elbows and mid-thighs. She had no indigestion and only occasional transient spells of diarrhea. The hemoglobin was 70% (Tallqvist) and the red cells, 3,900,000. She was eating a pound of liver 2 to 3 times a week, taking 9 capsules of "Extralin" a day and receiving an ampule of Lederle's extract intramuscularly in the buttocks once a week. Her subsequent blood counts were as follows, the hemoglobin being estimated by the Tallqvist method:

Date.	Hemoglobin, per cent (Tallqvist).	Erythrocytes, (in millions).
Dec. 1, 1933	75	4.65
8	75	5.00
15	80	4.54
22	75	3.90
26	75	4.50
29	80	4.40
Jan. 5, 1934	80	4.63
12	80	4.48
19	80	5.00
26	75	4.48
Feb. 2	70	4.20

On December 8 stained preparations of the blood showed nothing abnormal but slight achromia. A differential count was not made but the distribution of leukocytes seemed normal. Following the slight drop in the count on December 22, she received 2 ampules (6 cc.) of Lederle's extract a week, and 12 capsules of "Extralin" a day until January 12, when the former dose was resumed. During this time there was a slow but steady improvement in strength and her ability to use her extremities. Her tongue was practically normal, she had a good appetite, practically no gross incoördination of the upper extremities and could walk about the room with support. On January 26 she had a slight stomach upset with nausea and subsequently her appetite was poor. She had not made any change in her habits or taken any of the drugs that have been associated with the development of malignant neutropenia.

She awoke on the morning of February 4 quite tired and after her usual breakfast, vomited. Between then and noon she vomited several times. When seen at noon she looked pale and exhausted. Temperature, 102° F.; pulse, 110. Her throat was slightly red but not more than was to be expected from the vomiting. She was given an enema, a hot water bottle and a powder containing codein sulphate, $\frac{1}{4}$ gr., and acetylsalicylic acid, 7 gr., every 4 hours. She had a fair day and a good night. On February 5 she felt fairly well and was not seen. That night she vomited and retched most of the time and was very hot. When seen on the morning of the 6th she was in moderate shock and complained of a very sore throat. Her temperature was 99° F., pulse, 144 and respirations, 26. Her whole throat was bright red and covered with discrete patches of dry, gray white, tenacious exudate. There was practically no cervical adenopathy. The remainder of examination was negative except for marked dehydration. She was removed to the hospital where her blood showed hemoglobin, 65% (Dare); red cells, 2,830,000; white cells, 500, with 2% neutrophils and no visible platelets. The red cells themselves were remarkably normal. Swabs from her throat showed a few heterogeneous bacilli and cocci, no Vincent's organisms, only a few epithelial cells and no pus cells. Two cultures showed no diphtheria. She was given 10 cc. of pentose nucleotide and 6 cc. of Lederle liver extract intramuscularly, 1000 cc. of 10% glucose subcutaneously and normal saline per rectum. She was very weak and could retain nothing by mouth. Her temperature rose to 104° F., where it remained almost constantly. Her throat and neck remained much the same and except for moderate abdominal distention there were no other physical findings. The glucose was repeated every 8 hours and the nucleotide and liver extract every 6 hours. Blood transfusion was refused. On the night of February 6, blood examination showed hemoglobin, 60% (Dare); red cells, 2,800,000; white cells, 600, with no granulocytes. On the morning of the 7th the hemoglobin was 62%; red cells, 2,910,000; white cells, 500, with no granulocytes. In neither of the last two examinations could granular cells of any type be found on any of numerous slides. She gradually failed and despite stimulation with caffein, died on the morning of February 8.

Partial autopsy (Dr. T. D. Masters) 8 hours after embalming. "A fairly well developed and nourished woman weighing about 95 pounds and appearing about 62 years old. A midline incision was made and the lower half of the sternum and portions of the fourth and fifth ribs on the right side were removed. The gross appearance of these marrows was normal. Additional observations were made through this incision. The pericardium was smooth and glistening and contained about 30 cc. clear fluid. The heart was grossly normal. The various cavities and leaflets were normal to palpation. A portion of the myocardium was removed. The lungs were collapsed. The pleuræ were smooth and glistening. There was no fluid in the pleural cavity. The lungs were crepitant and air-containing everywhere. The liver was the usual size and shape. Its capsule was smooth and shiny. Its surface was yellow-green and firm and the edges were sharp. Because of the restrictions of the permit, no further examination was made."

Histologic examination (Dr. William Bloom, University of Chicago). "The sections of the lung and heart show nothing unusual. The liver tissue although badly preserved shows very prominent phagocytes attached to the walls of the sinuses, but without any evidence of increased phagocytosis such as occurs in some livers from pernicious anemia patients. No blood cell formation could be found and the blood cells circulating in the sinuses are exclusively erythrocytes and non-granular leukocytes; some of the latter, however, are quite large and suggested stem cells. The marrow from the ribs and sternum is exceedingly interesting. Erythropoiesis is proceeding in full blast. Many of the normoblasts have highly constricted polymorphous nuclei. Not a single granular leukocyte or myelocyte was found. The megakaryocytes are quite prominent and perhaps slightly more numerous than usual. Scattered through the parenchyma are more than a few plasma cells, frequently in groups. The stem cells are quite prominent with their basophil cytoplasm and prominent large nucleoli. One could not make a diagnosis of pernicious anemia from the sections in this case but the agranulocytic feature is quite prominent. Most of the marrows of agranulocytic angina have eosinophil myelocytes, but this marrow contained no myelocytes of any type."

Comment. Similar cases have doubtless occurred but are evidently rare, as I have been unable to find any record of them in the literature. Strumia¹ has reported the very interesting relationship between agranulocytosis and acute leukemia. There was no history of exposure to any of the physical or chemical agents or drugs known to produce neutropenia, nor of any previous infection which might have had a bearing on the disease. The examination of the bone marrow showed clearly that the primary defect was in the maturation of the myeloid series into granulocytic forms (Fitz-Hugh and Krumbhaar²). It also showed that the pernicious anemia had been adequately treated. Since, at the present time, we know of no substance which will produce or promote maturation of granulocytes there is no reason to suppose that any type of treatment would have availed in this particular case. Certainly such a case might shake one's faith in the possible efficacy of the treatment of a developed neutropenia by liver or liver extract.

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BOOK REVIEWS AND NOTICES

A MANUAL OF BIOCHEMISTRY. By J. F. McCLENDON, Professor of Physiological Chemistry, University of Minnesota Medical School. Pp. 381; 58 illustrations. New York: John Wiley & Sons, Inc., 1934. Price, \$5.00.

A CONDENSATION and revision of mimeographed material, this book presents unusual material in a somewhat novel manner. Of its six parts, the first, presents physico-chemical aspects of biology; the second, inorganic compounds; the third and largest section, organic compounds with biologic connections; the fourth, a short summary of the physiology of foods and metabolism; the fifth, about 50 pages of practical laboratory work; the sixth, a table of physical and physiologic properties of 1000 substances with biological connections. The individual reader must decide as to whether he likes his biochemical pabulum in such form. The illustrations cover a wide range, none too well. Presumably done in this fashion for the sake of economy, some might better have been omitted. Though hardly sufficient as a sole support to the neophyte, this book should be a valuable aid to many types of students. E. K.

THE PATIENT AND THE WEATHER. By WILLIAM F. PETERSEN, M.D. With the assistance of Margaret E. Milliken, S. M. Volume II. *Autonomic Dysintegration*. Pp. 530, lithographed; 249 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934. Price, \$6.50.

THE waggish comment by Mark Twain that "everybody talks about the weather but nobody does anything about it," is being refuted by this series of five or six volumes. The present belated one, follows Volume III and, seemingly, precedes Volume I. It concerns itself with headache, epilepsy, eclampsia and premature delivery, mucous colitis and gastric ulcer, the neuroses, urticaria, asthma, arthritis, glaucoma, ear, teeth, hair and therapeutic implications.

In general, the persons considered are those unusually responsive to their environment and termed by von Bergmann as "vegetatively stigmatized." Effects occur through changes in temperature, atmospheric pressure, vapor pressure and air ionization, bringing about either vascular spasm or relaxation, thereby affecting the blood supply to the tissues. Considering an acute infection such as appendicitis, it is stated: "actually the bacteria invade the organ after an anoxemic injury to the tissues. The sequence is not first bacterial penetration, then inflammation! On the contrary it is first tissue dysfunction—then invasion—and the combination of the two results in inflammation."

Many graphs are included and their comprehensiveness may be illustrated by one from a subject with arthritis, showing the metrograph, the clinical and subjective record and in addition the following curves for a 24-day period: Basal Metabolic Rate; Leukocyte Count; Methylene Blue Reaction Time; Respiratory Rate; Morning Temperature; Systolic and Diastolic Blood Pressure; Pulse Rate; Cholesterol; Phosphates; CO₂ Content; Blood pH; K/Ca Ratio; Potassium; Calcium; Serum Protein; Capillary Permeability; Blister Time. There is an abundant bibliography but no index. N. Y.

DISEASES OF THE RECTUM AND COLON AND THEIR SURGICAL TREATMENT. By J. P. LOCKHART-MUMMERY, F.R.C.S. (ENG.), M.A., M.B., B.C. (CANTAB.), Senior Surgeon to St. Mark's Hospital for Cancer, Fistula, and Other Diseases of the Rectum, etc. Pp. 605; 250 illustrations. Second Edition. Baltimore: William Wood & Co., 1934. Price, \$10.00.

IN the eleven years that have elapsed since this book first appeared, the advances in diagnosis and treatment have been so numerous that an extensive revision was obviously in order. This the distinguished author seems to have satisfactorily accomplished, and many will pardon to one of his position a dogmatism which at any rate conduces to clarity. The new chapter on precancerous conditions is a timely warning of the tendency of many benign neoplasms to become malignant. E. K.

THE NERVOUS PATIENT. A Frontier of Internal Medicine. BY CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University, Indianapolis. Pp. 453, Philadelphia: J. B. Lippincott Company, 1935. Price, \$4.00.

THE scope of this book is much more inclusive than its title would indicate. The author makes clear in his introduction that he has an individual approach to the "Nervous" patient, including in this category serious organic diseases, personality problems, disturbances of the internal secretions, psychoneuroses and mild insanity. He says, "to understand the 'nervous' patients, therefore, we must study not only purely functional conditions, but also the early stages of practically every physical and mental disease." Accordingly the author has presented 30 chapters in which he has included psychopathology, blood chemistry, allergy, the autonomic nervous system, organs, as the eye and ear, systems, as the respiratory and the gastro-intestinal, with certain organic and "nervous" manifestations found in each, the diseases encountered in neurology and psychiatry, including the psychoneuroses, disorders of sleep, disturbances within the sex life and suggested treatments for all.

Obviously, such an encyclopedia of medicine in 453 pages by one author is an ambitious project, and as such is likely to have deficiencies. He feels that the approach to the problem from the angle of psychopathology and by the psychiatrist is not the solution to the problem of the "nervous" patient. He says, "their field and ours overlap but little. Ours, none can enter save the internist trained in the accurate diagnosis of that great variety of organ dysfunctions which physical disease produces. He alone can evaluate those elements which the patient's disturbed personality injects into the clinical picture of organic disease; he alone can recognize those almost exact imitations of these same organic diseases which have their origin in the emotional life of the patient."

Yet, the author admits being untrained in the field of psychiatry. The inference, then, is that either he has peculiar acumen for discerning the interrelations of emotion and body functions, or the psychiatrist has spent his years of training for naught. Psychiatrists will often fail to agree with the author's optimistic concepts of certain entities such as Neurasthenia which he would define "as a well unified anxiety condition, developing as an incident in the previously efficient life of a person otherwise not psychoneurotic, based on some clearly recognized unwelcomed state, physical, social, economic, etc., all the psychic elements of which either are clearly in consciousness or easily can be brought there, and which, once relieved, shows no tendency to recur."

He invokes the various schools of psychopathology in understanding the

neurotic but largely rejects their views in treatment. Such severe neuroses as psychasthenia he would treat by, rest, routine, regular schedule, diet, Emerson's Essays, commitment of the Psalms to memory and the recital of one daily to his physician. He admits that some psychasthenias have been helped by psychoanalysis but that these must have been cases in which the patient merely accepted his disabilities.

There are some valuable suggestions in the understanding and management of the "nervous" patient, and occasional short case references. But the author's ambivalent attitude to psychopathology is unfortunate. He is repeatedly accepting, then rejecting its value etiologically in a manner that would be very confusing to the uninitiated reader who wished to get information for the understanding and management of the neurotic patient.

The author says that his book is intended for the general practitioner. It is written in a very interesting readable style, and for a survey of the author's own approach to medical problems it is well worth while. But it is not recommended for the reader who might infer from its title and the author's preface that it contained the most recent advances concerning the mental and physical disorders of psychogenic nature. O. E.

KORONARINFARKT UND KORONARINSUFFIZIENZ. In Vergleichender Elektrokardiographischer und Morphologischer Untersuchung. By Professor Dr. MED. FRANZ BÜCHNER, Vorstand des Pathologischen Instituts am Horst-Wessel Krankenhaus der Stadt, Berlin; Professor Dr. MED. ARTHUR WEBER, Vorstand des Balneologischen Universitätsinstituts in Bad Nauheim, Dr. MED. BERTHOLD HAAGER, Assistent am Balneologischen Universitätsinstitut in Bad Nauheim. Pp. 104; 116 illustrations. Leipzig: Georg Thieme, 1935. Price, Rm. 15.

ELECTROCARDIOGRAPHY seems now to have reached a development that requires specialized presentation. Only one field is covered in this book, the comparison of electrocardiographic and morphologic changes in coronary disease. Produced from the Horst Wessel Hospital with the aid of the Notgemeinschaft der Deutschen Wissenschaft, this work in its introduction shows a refreshing acquaintance with the contributions from other countries and a willingness to accord them proper significance. It is regrettable, however, that more experimental findings, the recent work on the Thebesian System and Leary's two types of coronary disease were not included, even in this short space.

Two-thirds of the book is made up of the data on 43 cases (protocols on the left, electrocardiograms, photographs of the heart, and diagrams of the lesions on the right). This constitutes evidence of permanent value. The labor required from the reader in making interpretations will be amply repaid him. E. K.

ECONOMIC PROBLEMS OF MEDICINE. By A. C. CHRISTIE, M.S., M.D., Professor of Clinical Radiology, Georgetown University Medical School, etc. Pp. 242. New York: The Macmillan Company, 1935. Price, \$2.00.

THIS little volume is from the pen of a practising physician who was a signer of the minority report of the Committee on Costs of Medical Care. Early chapters concerned with the economic aspects of Medical Education, private and hospital practice including the training of specialists, the relation of the physician to medical organizations and the community are all reflections of the viewpoint of the average intelligent physician. They may well be considered as supplementing discussions of these subjects in "Medi-

cal Care for the American People," a work which reflects the attitude of professional sociologists.

The author also presents an analysis of medical care under Workmen's Compensation laws, contract practice and the various forms of Health Insurance in vogue in Europe. His views on these subjects differ from those of the extreme liberal and the sociologist but are set forth without emotional display, for which he is to be congratulated. He further supplements the much discussed "Medical Care for the American People" by describing modest attempts which have been started in a number of communities as local solutions to the vexing problems of providing adequate care to all people at a reasonable price and with due regard for community responsibility for its indigent. The author's suggestions and requirements for a comprehensive plan for medical care will probably not please the ultra conservative physician who wishes nothing changed and will certainly not satisfy the professional sociologists who wish to change everything and who seem unwilling to await an orderly evolution. It will appeal to the thoughtful person, whether layman or physician, who prefers moderation in a discussion of what is undoubtedly the most important medical problem of our generation.

E. T., JR.

MANUAL OF DIABETES. By J. J. CONYBEARE, M.C., M.D., OXON., F.R.C.P., Physician to Guy's Hospital. Pp. 123. New York: Oxford University Press, 1935. Price, \$2.00.

THE need for a thorough knowledge of the practical details of diabetic treatment on the part of the patient as well as the physician receives full consideration in this book. In fact, information of this kind has been summarized in a lengthy appendix which, as the preface tells us, is sold separately at low cost. The main text is on the whole successful in its aim "to outline in concise form the general considerations which govern the physician's treatment of diabetes," though many a physician will be disappointed in not finding fuller treatment of some detail on which he wants more information.

E. K.

NEW BOOKS.

The Doctor's Bill. By HUGH CABOT. With an Introduction by A. LAWRENCE LOWELL. Pp. 313. New York: Columbia University Press, 1935. Price, \$3.00.

Geschichte der Physiologischen Chemie. By DR. FRITZ LIEBEN, Privatdozent an der Universität, Wien. Pp. 741. Wien: Franz Deuticke, 1935. Price, M. 20.

Some Notable Epidemics. By H. HAROLD SCOTT, M.D., F.R.C.P. (LOND.), D.P.H., D.T.M. and H. (CAMB.), F.R.S.E., Assistant Director, Bureau of Hygiene and Tropical Diseases. With a Preface by W. W. JAMESON, M.A., M.D., F.R.C.P., Barrister-at-Law, Professor of Public Health in the University of London; Dean of the London School of Hygiene and Tropical Medicine. Pp. 272. Baltimore: William Wood & Co., 1934. Price, \$4.75.

Medizinische-chemische Bestimmungsmethoden. Eine Anleitung für Studierende der Medizin und für Laboranten. By KARL HINSBERG, Vorsteher der Chemischen Abteilung des Pathologischen Instituts der Charité, Berlin; Privatdozent an der Universität Berlin. Volume 1. Darstellung der allgemein gebräuchlichen und der wichtigsten quantitativen Methoden. Pp. 93; 29 illustrations. Berlin: Julius Springer, 1935. Price, Rm. 4.80.

- The Cosmic Way to True Civilization Through Parenthood.* By GEORGE H. DONAHUE. Pp. 68, n.p., 1934. (No price given.)
- Syphilis. Ihr biologischer Ursprung und der Weg zu ihrer Ausrottung.* By DR. MED. FERDINAND THUGUT. Pp. 109. Stuttgart: Ferdinand Enke, 1931. Price, Rm. 4.00.
- Clinical Management of Syphilis.* By ALVIN RUSSELL HARNES, M.D., Chief of Congenital Luetic Clinic, New York Hospital. Pp. 71; illustrated. New York: The Macmillan Company, 1935. Price, \$1.50.
- Fifty Years a Surgeon.* By ROBERT T. MORRIS, M.D. Pp. 347. New York: E. P. Dutton & Co., Inc., 1935. Price, \$3.50.
- Manual of Diabetes.* By J. J. CONYBEARE, M.C., M.D. (OXON.), F.R.C.P., Physician to Guy's Hospital. Pp. 123. New York: Oxford University Press, 1935. Price, \$2.00. (Review, p. 119.)
- Emotions and Bodily Changes. A Survey of Literature on Psychosomatic Interrelationships, 1910-1933.* By H. FLANDERS DUNBAR, M.D., PH.D., Departments of Medicine and Psychiatry, Columbia University. Pp. 595. New York: Columbia University Press, 1935. Price, \$5.00.

NEW EDITIONS.

- Electrotherapy and Light Therapy.* By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, Polyclinic Medical School and Hospital, New York; Physician in Charge Physical Therapy, City Hospital, New York, etc. Pp. 696; 263 illustrations and 1 colored plate. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, \$7.50.

This successful attempt to show the practitioner the possibilities and limitations of physical therapy deserves its reputation as the best book on the subject in English. This edition adds a new chapter on the physiologic effects of electricity, together with new material on iontophoresis, the physics and use of thermionic tubes, diathermic hyperpyrexia and so on. Electrosurgery and light therapy have demanded especial additions.

- The Biochemistry of Medicine.* By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital; and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 518; 31 illustrations, 17 tables. Second edition. Baltimore: William Wood & Co., 1935. Price, \$6.00.

"This book is designed both for the student of medicine receiving clinical instruction in the later years of his course, and for the physician who received no special instruction in the medical applications of biochemistry. In this new edition the chapter on the endocrine secretions has been largely rewritten, and a brief account is included of the important discovery of anti-endocrine compounds New subjects dealt with briefly include von Gierke's glycogen disease, the diseases concerned with incorrect lipid storage, tyrosinosis, the dinitrophenol treatment of obesity, the glycine treatment of myasthenia gravis, and the pentose-nucleotid treatment of agranulocytosis." The summary at the end of each chapter is a valuable feature, if properly used.

- Handbook of Anesthetics.* By J. STUART ROSS, M.B., CH.B., F.R.C.S.E., Late Lecturer in Practical Anæsthetics, University of Edinburgh, and H. P. FAIRLIE, M.D., Anæsthetist to the Western Infirmary, The Royal Hospital for Sick Children and the Dental Hospital, Glasgow. With a chapter upon Local Anæsthesia by W. QUARRY WOOD, M.D., F.R.C.S.E., Assistant Surgeon, Edinburgh Royal Infirmary. Pp. 299; 66 illustrations. Fourth edition. Baltimore: William Wood & Co., 1935. Price, \$4.00.

Dr. Fairlie, whose name first appeared on this book in the previous edition, now assumes sole responsibility; emphasis, however, continues to be laid upon first principles. New methods and new apparatus have been conservatively added; ether (including 2 lines on divinyl ether) occupies but 30 pages and chloroform a paltry 17. The chapter on the choice of anæsthetic is valuable and could well have been further extended.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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RECENT ADVANCES IN PERIPHERAL VASCULAR DISEASE.

IN recent years investigation in peripheral vascular disease has grown rapidly. The increasing attention to these disorders is reflected in the remarkable growth of the number of clinics established for their study. This shift in interest from the central to the peripheral vascular system has led to the development of a tremendous literature upon the subject.

Etiology. *Arteriosclerosis.* The work of Popoff¹ on the digital vascular system points directly to changes of etiologic importance in the peripheral arteriovenous anastomoses in diabetic and arteriosclerotic gangrene. The arteriovenous anastomoses, which he terms the glomic system, are described in detail, with their local and general functions. Comparative studies of the glomic system in arteriosclerotic and diabetic gangrene show that both depend upon a sclerotic process and contrary to present views the two processes are not identical. In arteriosclerotic gangrene the changes are due primarily to hyalin degeneration in the afferent artery of the glomus, whereas in "diabetic gangrene the intima of the Sucquet-Hoyer canal (the arteriovenous anastomosis proper) and that of the preglomic arterioles are the first to show signs of primary degenerative changes, while the intima of the afferent artery of the glomus remains intact. These changes bring about an understanding of the trophic and vascular changes observed in the digits."

The dissections of Wollard and Weddell² in patients with diabetic and arteriosclerotic gangrene also demonstrated distinct differences in these two processes. They injected the arteries of amputated legs and made arteriolar counts at various levels in the foot. In senile gangrene no transformation or new formation of arterioles occurred, but in diabetic gangrene there was a tendency for the arterioles to increase in both these ways. In senile gangrene the finer vessels actually tended to disappear. In thrombo-angiitis obliterans the tendency for these vessels to increase was at a maximum.

Raynaud's disease is described as a localized form of vasoconstrictor disturbance characterized by clinical phenomena dependent upon excessive constriction of small vessels. Lewis and Pickering³ have recently published evidence to show that the term Raynaud's disease has not

been suitably defined, and that it probably cannot be defined to common agreement. These authors feel that there may be several or many quite distinct maladies grouped under the term. That this is undoubtedly true in general usage was shown by Allen and Brown⁴ in an excellent review applying the criteria of Raynaud to published cases. Observations of Raynaud's own case reports showed a lack of correlation with his criteria in some instances.

Lewis and Pickering use the term "Raynaud's phenomenon" to describe closure of arteries of the size of the digitals with resulting discoloration of the part. Closure may occur with or without local nutritional changes. While cooling of an artery causes narrowing due to vasomotor constriction and direct response of the vessels, experimentation showed that vasomotor constriction alone was not sufficient to close the digital artery. Closure was ascribed to a local fault, the nature of which is still obscure. This concept ascribes the phenomenon of Raynaud's disease to the bloodvessel itself and not to the nervous system. The fact that cooling would not produce changes when the vasomotor nerves were sectioned was attributed to insufficient cooling, without vasomotor tone.

Sixteen of 33 cases of intermittent spasm of the digital arteries (dead finger, for example) gave a family history which lead Lewis to believe that this phenomenon may often be an inherited peculiarity. The fact that some cases with scleroderma showed skin hardening preceding the attacks cast doubt upon the skin changes always being secondary to the vasospastic changes, and justified another group. Cases developing after injury, vibration, working on air pressure drills and so on, he believed constitute another yet obscure group. He did not ascribe those cases with bilateral massive gangrene of the ends of the fingers to continuous spasm of the arteries. "The attack is too prolonged and areas involved too sharply defined and unvarying, and the vessels could not be opened by warmth or other means as with all undoubted cases of spasm. Evidence of obstruction in the digital vessels has been shown in these cases and there is no evidence to support the idea that the thrombosis could result from the spasm." Reactive hyperemia would prevent it also. Furthermore, spasm is known to occur in association with other types of organic obliterative disease. The authors point to the problem of spasm as a determining factor in intimal or thrombotic changes with resulting obstruction in small arteries, as a subject for future study.

Thrombo-angiitis Obliterans. The etiology of thrombo-angiitis obliterans remains unknown. Although most workers hold one of two main theories, other theoretical explanations have been brought forward as possibilities. The diversity of opinion itself is the best evidence of the ignorance of the cause of thrombo-angiitis obliterans. The infectious theory with toxin formation and spread, based chiefly on transplantation experiments, has found no bacterial support. In Popoff's¹ study of the arteriovenous anastomosis of the digit in thrombo-angiitis obliterans he found no support for inflammation or thrombosis of the vessels as a causative agent. He states that the glomic system (the normal arteriovenous anastomosis in the digit) appeared to be free from primary specific changes and describes a "hitherto unknown vascular anomaly of the peripheral digital system" as a cause of the trophic

and inflammatory changes. This abnormality is the presence of an anastomosis between the arteries and veins, differing from the usual type in size, structure and topographic distribution. In his normal and pathologic material covering 840 individual blocks studied by serial sections, he found these abnormal anastomoses only in cases of thrombo-angiitis obliterans. He suggests that "comparative results of studies on the digital glomus demonstrate that neurovascular and trophic changes observed in the digits in many instances may be due primarily to local changes in the glomus and not to inflammatory degeneration or obstructive changes in the large arteries and veins of the extremity. In looking over descriptions of symptomatology in thrombo-angiitis obliterans it is significant that local chronic cyanosis of the toes may precede gangrene of the foot by months and even years and may be the only objective sign. Postural color changes in the earliest stages occur only in the tips of toes."

Confirmation of Popoff's work would modify completely the conception of thrombo-angiitis obliterans.

The use of tobacco as a cause of thrombo-angiitis obliterans has been a subject of much study. The reviewer finds no reports that increased smoking among women has increased the percentage of cases found in women. The report by Maddock and Collier⁵ of diminished skin temperature following smoking of cigarettes, recently confirmed by Johnson and Short,⁶ added impetus to this theory. The allergists, too, have continued attempts to correlate allergy, tobacco and thrombo-angiitis obliterans. Sulzberger⁷ found that 78% of 79 patients with thrombo-angiitis obliterans had immediately positive skin reactions to tobacco extracts, but also did 36% of smokers without thrombo-angiitis obliterans and 16% of the non-smokers tested. Prausnitz-Küstner antibodies were found in only 1 case. Sulzberger states that, as the positive tests in patients with thrombo-angiitis obliterans correlated with clinical evidence incriminating tobacco, his results were highly suggestive that sensitization of the vascular system to tobacco may play at least a contributory rôle in many cases. Harkavy and Romanoff⁸ conclude that the strikingly larger number of positive skin tests to tobacco in thrombo-angiitis obliterans (69%), compared to 11% in controls, indicate that tobacco is the dominating reacting allergen in thrombo-angiitis obliterans. Chobot,⁹ however, found many reactions in allergic children who never smoked, one being in a child of 3. Of 53 asthmatic children from 3 to 12 years of age, only 6 (11%) were negative. The results were presented to emphasize caution in interpretation of the diagnostic tests. Their significance is not known, but Chobot believes it is analogous to what is seen when patients are tested with solutions of morphin and histamin.

To demonstrate the diversity of opinion in the etiology of thrombo-angiitis obliterans, although published 4 years ago, one may mention the work of Kaunitz¹⁰ on chronic ergot poisoning. A study of the literature of epidemic ergotism convinced Kaunitz that the cause of some vasomotor and trophic disease could be traced to endemic ergotism. Obviously this theory has not been proved. All the evidence is indirect. It has long been known that males are more susceptible to ergot poisoning than females and that ergotism produces gangrene in young and middle aged males but rarely in females. It has also been shown that

the rye fields of this country are often contaminated, and that grains from some fields are infected so heavily "that every head may have one, or more sclerotia." Kaunitz also quotes Morgan in a description of an epidemic of ergot poisoning in England in 1928. Symptoms occurred only in Jews who ate rye bread. These data, while interesting, are not convincing, and are offered in this light only.

In a report of 2 cases of thrombo-angiitis obliterans occurring in women, Silbert¹¹ again reviews the possibility of the dependence of thrombo-angiitis obliterans upon a constitutional hereditary factor. Evidence of horizontal and vertical inheritance is very meager in reported cases, but the great preponderance of cases in males and in the Hebrew race surely suggests such a sex-linked constitutional factor.

Sporadic efforts to associate etiologically thrombo-angiitis obliterans and thrombophlebitis migrans have been made, but usually the latter has been considered a separate disease. Many cases have been reported without any apparent arterial disease. However, phlebitis as a manifestation of thrombo-angiitis obliterans is well known. d'Abreu¹² in England reported a case, clinically thrombophlebitis migrans for 40 years, which developed arterial symptoms and at postmortem proved to be one of thrombo-angiitis obliterans.

Periarteritis Nodosa. The view that periarteritis nodosa is a manifestation of syphilis has long been discarded. The course and nature of the disease suggests infection as a cause and a gamut of such causes has been offered. The filterable virus theory has many adherents, but the work of Friedberg and Gross¹³ in which 4 of 8 cases autopsied presented conclusive evidence of rheumatic heart disease appears significant. Attention to a possible relationship between periarteritis nodosa and rheumatic fever has been made before. However, the rigid criteria of the presence of Aschoff bodies in the myocardium and other manifestations of rheumatic fever, associated with the typical findings of periarteritis nodosa have not been used. Arterial lesions usually described in rheumatic fever have other characteristics.

Erythromelalgia. Lewis¹⁴ has abandoned the term erythromelalgia. He believes that a number of diseases, including cases of thrombo-angiitis obliterans and other arterial diseases, have been placed in this diagnostic pigeon-hole because of the symptom of burning pain. This type of pain describes a "susceptible state" of the skin. This is a local affair, produced by friction, warmth, and dependency of the part, which, when combined with redness on dependency, usually leads to the diagnosis of erythromelalgia. Lewis and Hess¹⁵ have previously shown that a skin injured in any way may enter this susceptible state, become hyperalgesic, with the threshold of heat lowered, and when the temperature passes 32° to 34° C. develop burning pain.

The final criterion for the diagnosis of erythromelalgia has been a vasodilatation, generally considered of vasomotor origin, which often produces a venous pulsation and an objective increase in the temperature of the part. Color may deepen without active dilatation, so that color change alone does not signify active hyperemia. Lewis found there was very little in reported cases to indicate that the temperature of the part was greater than one would expect in any limb under similar circumstances, and no objective evidence appeared to support the presence of abnormal vasodilatation. There is, therefore, no evidence

that abnormal vasodilatation based on vasomotor phenomenon must occur. The skin is in the abnormal condition, Lewis states, and when an increased blood flow raises the temperature to the proper level, burning pain results. There is no evidence that abnormal dilatation is necessary. Lewis believes that the term "erythromelalgia" should be discarded as a term to designate a disease and that some other term such as "erythralgia" should be employed to designate the painful redness of the skin.

Diagnosis. *Subjective Findings.* Goldsmith and Brown¹⁶ have offered a tentative classification of the pain in thrombo-angiitis obliterans which is helpful in the diagnosis of the immediate cause of the pain, and consequently helpful in the institution of treatment against the offending etiologic agent. The classification is based upon an analysis of 100 cases. Pain is divided into two major groups: (1) pain on exercise, and (2) pain at rest. Pain dependent upon exercise may arise from phlebitis or intermittent claudication, the characteristics of which are well known. Rest pain is of several distinct types. So-called pre-trophic pain may be well localized in the feet and hands, is burning in character, worse at night, and aggravated on dependency. This type appears to correspond to the erythralgia of Lewis.¹⁴ The term pre-trophic is used because ulcers and gangrene are prone to develop at the site of pain. Trophic pain, that of ulcer and gangrene, develops gradually, is often severe, is stinging and burning in character, and is accompanied by hyperesthesia of the part. The characteristics of the pain of inflammation vary with the location. Arteritis sometimes leads to an aching, generalized pain with, of course, coldness of the part, while phlebitis leads to a more localized form with tenderness over the veins and exacerbations on exercise. Acute occlusion with massive ischemia causes a sudden tenderness at the site of occlusion with severe generalized pain radiating peripherally. The last classified type, ischemic neuritis, is very severe, diffuse, and extends over large areas not always corresponding to the distribution of the nerves. It is a paroxysmal, tearing pain, which may radiate from one end of the extremity to the other. Skin discoloration may be associated. Exacerbations may last several hours and the pain itself may be present irregularly for 1 to 8 months. Neurologic studies in these cases may show changes in reflexes and sensory nerves.

Physical Examination. Great stress has been laid upon the palpatory findings in the differential diagnosis of vasospastic and organic occlusive disease. The importance of establishing definitely the normal variations in palpatory findings in the absence of disease, as a groundwork for interpretation of the abnormal, has led Reich¹⁷ to study the arterial network in the lower extremities in 500 healthy individuals. He found an absence of the dorsalis pedis pulse in 4%, absence of the posterior tibial in 5%, and in 8% the dorsalis pedis was found in a location outside the usual position. The study was continued with a dissection of the arterial system of the lower extremity in 70 legs of 35 white cadavers. It was found that the vessels below the knee presented many variations from the usual picture found in textbooks of anatomy. Fifty-two (74%) of the limbs had predominant dorsalis pedis arteries; in 5 (7%) the lateral tarsal artery was the larger and in 10 (14%) the lateral tarsal was the main artery of the dorsum of the foot. In 7 cases the dorsalis

pedis was very small and in 3 was entirely absent. The author offers as an explanation for these unusual variations the phylogenetic development of the human, and states that "it is plainly due to the relative recent transformation in vascular pattern of the human leg and foot that the arterial channels of the dorsum present so variable a character." The posterior tibial arteries in the same study were absent in 4 legs (6%) and in 2 (3%) were very small. The phylogenetic explanation is extended to these vessels as well. Both tibials and the peroneal are described as of recent origin, and in man alone of all primates it is stated we find the complete pattern of new connections between the popliteal and the arterial supply of the dorsum and sole of the foot.

It is probably true, then, from Reich's statistics that in 100 extremities with no occlusive peripheral vascular disease the usual palpation in the anatomic location of the dorsalis pedis would disclose a pulsating artery in approximately 80. In 14 of these trials it would be necessary to palpate more laterally in the region of the head of the third metatarsal bone. In about 4 of the legs the possibilities of feeling a pulsation in both regions would exist, but with small arteries this might be difficult to determine. In a like number no pulsation at all would be found. For the posterior tibial, approximately 3 of 100 limbs would show a very weak pulsation and 3 to 5 no pulsation at all.

Certain other factors as well may make palpation of the arteries difficult. Edema, adiposity, and ligamentous attachments, especially in the case of the posterior tibial, sometimes add to the diagnostic handicaps. One must agree from this work that, although palpation of the arteries of the foot is a most important diagnostic procedure, the absence of a pulsating artery is not pathognomonic of disease and other evidence must be on hand for diagnosis, especially in doubtful cases.

That thrombo-angiitis obliterans is not exclusively a disease of the extremities, and may add to diagnostic difficulties elsewhere, finds further support in 2 recent reports.^{18,19} Averbuck and Silbert, in a study of the causes of death in thrombo-angiitis obliterans have shown that coronary, mesenteric and cerebral thrombosis are not uncommon, and that their occurrence in thrombo-angiitis obliterans is not merely coincidental. Of 47 cases 22 died of vascular accidents.

Roentgenography. Search for objective findings to confirm a diagnosis of peripheral vascular disease often leads to attempts to demonstrate calcium in the arterial wall roentgenologically. The clinical significance of such findings in occlusive disease, however, has not been satisfactorily established. One finds sporadic reports of occasional cases²⁰ in which the more marked calcification occurred in the opposite or non-symptomatic side. Lansbury and Brown²¹ have investigated this problem recently to clarify the questions of the clinical importance of calcification, the possible correlation between calcification and clinical arterial occlusion, and the possibility of determination of the nature of the occlusive process by the presence or degree of calcification. Studies were carried out on a group of clinically negative controls from 50 to 80 years of age, a group with arteriosclerosis obliterans, and a group with thrombo-angiitis obliterans. Results were interesting and enlightening. In arteriosclerosis obliterans the findings closely paralleled the control series with the curve of incidence of calcification in the various age

groups quite similar, but slightly higher in occluded cases. Calcification in the age period from 65 to 70 years was greatest in both groups. Results indicated that calcification after the fifth decade was probably a normal process and consequently occlusion may or may not be superimposed upon it. In grading the degree of calcification it was found that no significant correlation could be obtained between the degree of calcification and the presence of occlusion, except when calcification was entirely absent, when the chances of the arteries being open or closed were 70% to 30%.

In thrombo-angiitis obliterans calcification was less frequent than in either of the other groups for similar age periods. In this disease for example, at 54 years of age, calcification occurred in 14% of the patients, in the controls in 40 to 50%, and in arteriosclerosis obliterans in a somewhat higher percentage. In differentiating the latter disease from thrombo-angiitis obliterans one might say, then, that calcification as shown roentgenologically may be of some value. However, demonstration of calcification does not give objective evidence favoring the presence or absence of occlusion and one must guard against erroneous conclusions from its presence. In the opinion of Lansbury and Brown degenerative changes, intimal thickening, and medial calcification can diminish the lumen of arteries but do not progress to a stage of complete occlusion in the larger arteries, and calcification alone without an occluding thrombosis is not clinically significant.

Postmortem observation of the arterial lumen may lead to false conclusions in arterial patency. Stewart, Birchwood and Wells²² emphasize that in dissecting the coronary arteries one often notes that plaques appear to impinge markedly upon the arterial lumen but that when these arteries are placed under a tension comparable to that of the systemic blood pressure the apparent narrowing may disappear and the integrity of the blood column be maintained. Roentgenographic confirmation of these changes were obtained by injection of the coronary circulation of excised hearts with radio-opaque media.

Clinical arteriography, the use of radio-opaque media by intra-arterial injections into the living human, is gaining ground as a diagnostic procedure.²³⁻²⁷ Allen and Camp²⁶ have considered its diagnostic value and evaluated the method in reference to the entire group of peripheral vascular cases. They have found that approximately 85% of such cases can be correctly diagnosed by a good history and thorough physical examination. Increases in this percentage depend upon special methods of study, capillary microscopy, oscillography, skin temperature studies, color changes to posture and the other special tests. After use of these procedures a small number of cases remain in which arteriography is the most important diagnostic aid. While most cases do not require the procedure, it is extremely important in those few not diagnosable otherwise. This is exemplified in thrombo-angiitis obliterans when the obliteration is in the small digital arteries. The method demonstrates the extent and location of collateral circulation, the location and extent of the disease, and the nature of the pathology, not only for diagnosis but as a guide to prognosis and treatment as well.

Vasodilating Procedures. In the past 10 years the methods for determination of spasm of bloodvessels have increased markedly. Not only have these methods made possible differentiation of doubtful

cases of vasospastic and occlusive disease but they have also made possible the determination of the extent of vasospasm present in occlusive disease. In thrombo-angiitis obliterans, for example, spasm may play a dominant or minor rôle in the symptomatology. If important in the symptomatology, operative procedures for relief of spasm are very effective therapeutic weapons, but if spasm is of minor importance these operations give little relief. As a consequence diagnosis of the physiologic state of vasospasm may be more important in instituting therapy than the anatomic diagnosis of thrombo-angiitis obliterans.

A discussion of the well established methods for the estimation of vasospasm does not constitute a part of this review. Procedures in general use depend upon an interruption of the vasoconstrictor nerves between the parts supplied and the central nervous system. The more important methods are local anesthesia, sympathetic ganglion block, spinal anesthesia, artificial fever by typhoid vaccine, or wrapping patient in blankets, heating of the hands or feet, Roentgen ray to the lumbar region, and the use of drugs. The release of spasm is measured indirectly by determinations of skin temperature.

All these methods are not of equal value. The heating of the body or extremities, for example, while relatively simple and without hazard is not as effective as spinal anesthesia or high fever. Pickering and Hess²⁸ have noted that warming the body of normal subjects produces vasodilatation more easily in the hands than in the feet. This delay occurred when the extremities were exposed to temperatures below that of the body and the onset was delayed in cool hands or feet or in one cold digit. The fine localization of the changes on cooling a part tend to rule out sympathetic action and favor the local action of cold on the vessels as the cause, so that when the body and digits are cool the vessels are constricted both by sympathetic tone and by a direct action on the vessels. It is the direct action which delays the response on cooling. Observations also suggest that warming removes only a part of vasoconstrictor tone from the feet, the remainder being permanent unless the sympathetics are blocked. This change explains the failure of vasodilatation in the feet as compared with the hands. The difference in response of the fingers and toes is important clinically, for with this test an incomplete response cannot be used as indication of the presence of disease.

Shaw²⁹ believes that the estimation of skin temperature rise is diagnostically useful in vasospasticity of the dermal bloodvessels and is particularly applicable to Raynaud's and other purely spastic conditions. However, in occlusive disease, such as thrombo-angiitis obliterans, he believes it of only slight value because of possible error, because considerable hyperthermia is not necessary for the relief of symptoms or the healing of peripheral lesions, and because, although vasospasticity exists in the surface bloodvessels, ganglionectomy is unable to overcome the effects of a complete block of the deeper vessels.

Miscellaneous Procedures. Recently Bernheim³⁰ has published a preliminary report on a simple technique for the interpretation of bloodvessel disease of the legs. The patient sits with the legs crossed and the small swing of the foot, which is synchronous with the cardiac cycle, is recorded on a moving drum by a rod fastened to the shoe. Bernheim believes this method reveals accurately the state of the cir-

culatation in the leg and not pulsations from any one particular artery such as the popliteal. Until further work is done to establish the efficiency of the method one must withhold opinion as to its possibilities.

Therapy. Advances in therapy in peripheral vascular disease have kept pace with, and to a great extent have depended upon, the improved diagnostic procedures.

General Procedures. Samuels³¹ has reported results in thrombo-angiitis obliterans with a method of treatment he had described previously. The routine is marked by extreme conservatism, which he regards as obligatory. In over 300 patients in 8 years he has found only one requiring amputation. This constitutes less than 1% as compared with 14% or more in the work of others. It is the adherence to a general outline of therapy, "an intelligent combination of various fundamental factors," which assures success. Briefly the procedure consists of: (1) bed rest; (2) abstinence from smoking; (3) intravenous saline injections, and (4) local treatment of ulceration and gangrene. Bed rest he believes absolutely essential. The lower extremities must be horizontal. This position controls edema, which even if very localized, retards healing and may be the one factor which causes ulceration to persist. Smoking he considers harmful. Evidence for this is given in the section on etiology above. Samuels cites the clinical course of gangrene as he has seen it in tobacco users as the criterion for withholding tobacco. Intravenous saline injections are used to lower blood viscosity upon the basis of previous work by Mayesima, Koga, Willy Meyer, Silbert and others. An outline of the technique used is given. Local treatment of ulceration and gangrene is carried out by adherence to correct surgical principles, in order to aid in formation of a line of demarcation, to control pain and to maintain asepsis. It is important, he states, to control the pain of gangrene until the acute process subsides to avoid unnecessary amputation. Samuels feels that sympathectomy and ganglionectomy have no place in the treatment of thrombo-angiitis obliterans. He has found no cases of massive gangrene healed by these methods, and the small ulcers or areas of gangrene so treated he believes have healed because of the confinement to bed postoperatively.

Drugs. Theobromin, because of its vasodilating properties centrally, has been used in peripheral vascular disease. Scupham,²⁰ who used the drug previously with some success in thrombo-angiitis obliterans, has extended his observations to arteriosclerosis with intermittent claudication, Raynaud's disease and allied vasospastic disorders. The latter group showed no improvement, but arteriosclerosis and thrombo-angiitis obliterans with a large element of spasm responded sufficiently well to consider the drug a valuable adjunct in their treatment. Best results were obtained with theobromin-sodioacetate. Newell and Allen,³² however, found best results with theobromin sodiosalicylate when given intravenously. Results orally were inconstant. Their conclusions were similar to Scupham's in that the drug was described as of little value in treatment of peripheral vascular disease except as an adjunct.

Kovács³³ in this journal applied the use of acetyl beta-methylcholin to vasospastic disease by iontophoresis. This method does not permit definite knowledge of the dosage given. How much of the drug is absorbed into the skin and how deeply it penetrates remains for future

investigation. The effect is considered to be due to deposition of the drug in the superficial tissues and a low absorption with prolonged vasodilatation. The skin temperature, where spasm of the peripheral vessels was present, increased 4° to 10° for 2 to 4 hours. The place of this technique in treatment of vascular disease, like that of theobromin, is still doubtful.

Barker and Brown,³⁴ also in this journal, have reported a definite lengthening of time necessary to produce intermittent claudication during a standard claudication test in 92% of 55 cases of thromboangiitis obliterans and arteriosclerosis obliterans following the intramuscular injection of a pancreatic tissue extract. Similar effects were noted in 8 cases of thromboangiitis obliterans after intramuscular myoston, a skeletal muscular extract. Myoston, however, was beneficial in only 1 of 5 cases of arteriosclerosis obliterans. In the cases benefited no significant rise in skin temperature was noted, indicating that the results were not due to vasodilatation but, to theorize, probably through supplying some substance to actively contracting muscle, the result of direct action on the ischemic muscle.

Starr³⁵ also in this journal investigated the effect of three factors, heat, desiccation and oxygen, in the treatment of peripheral vascular disease, especially in acute occlusion. He found, with the use of a constant temperature foot cradle, that the optimum temperature for relief of pain was 33° to 35° C., approximately that of the skin in the lower extremities when vessels are fully dilated. Higher temperature, which might be beneficial to a foot with a normal blood supply, often caused intense pain. The temperature range 33° to 35° C., Starr believes, acts when the normal mechanism is lost by keeping the temperature of the tissues at the level at which they are accustomed to function. While use of oxygen applied locally can relieve pain and change skin color, through its penetration of the skin, results were insufficient to advocate its routine use.

Vasomotor Denervation. Besides the general principles of avoidance of injury and infection, warmth, baths, exercises, use of drugs and other procedures mentioned previously, those procedures described in diagnosis of spasm have been used to relieve vasospasm for therapeutic reasons. The simpler of these methods are more valuable in demonstrating results which can be made permanent by the more serious techniques, such as ganglionectomy and sympathectomy. Brown, Craig and Adson³⁶ have recently reviewed the criteria for selection of cases for these more serious operations. They reemphasize that the rationale of the use of operation on the sympathetic nervous system in occlusive disease is based upon previous demonstration of high degrees of vasoconstriction in the non-occluded major and collateral vessels. Use of ganglionectomy depends almost entirely upon proper selection of cases on this basis. The other factor is the clinical aspect of the case. Emphasis is also placed upon the fact that thromboangiitis obliterans is a disease with a variable clinical course and after ganglionectomy thrombosis may continue to occur, for there is no definite proof that such operations prevent its occurrence.

While Brown, Craig and Adson state that in 8 years of use they have had conclusive demonstration of maintained and permanent vaso-

dilatation of the peripheral arteries with ganglionectomy, Smithwick, Freeman and White³⁷ have observed recurrences of vascular spasm after complete sympathectomy in Raynaud's disease. They do not attribute the results to a local fault as Lewis has described it, but believe from experimentation that the vascular spasm is a result of sensitization to adrenalin of the sympathectomized extremity. In these cases care was taken to insure a complete interruption of the sympathetic pathway so that the results cannot be explained on incomplete surgical interruption of the pathways, nor on regeneration. Results were more permanent in the lower extremities. Reappearance of symptoms occurred on exposure to cold and also in response to pain and emotional stimuli, which suggested the possibility of a direct action of adrenalin upon the bloodvessels. Hypoglycemia, which also mobilizes adrenalin, produced the same results. Intravenous adrenalin in doses which produce in the blood a concentration similar to that in physiologic response of endogenous adrenalin caused a rapid fall in surface temperature in the sympathectomized extremity. The normally innervated or partially sympathectomized parts showed no remarkable changes. Further work on animals is necessary to establish the results and to explain the discrepancy between results in the upper and lower extremities.

Parathyroidectomy. Bernheim and Garlock,³⁸ as a result of observations to be reported later, have formed the opinion that calcium metabolism is an important factor in Raynaud's disease and other vasospastic states. A mechanism of production of vasospastic phenomenon by defective calcium metabolism is not evident. They have subjected 6 patients with Raynaud's disease and scleroderma to parathyroidectomy, who were not benefited by conservative treatment. Following operation they noted marked relief of symptoms. Pain was relieved and skin color changed within 24 hours, the best results occurring in uncomplicated Raynaud's disease. In scleroderma the skin became noticeably softer with partial return of function in fixed joints.

Suction and Pressure in the Therapy of Peripheral Vascular Disease. Until recent months, in the absence of spasm in occlusive disease of the arteries, there has been no method by which blood flow could be increased. True, attempts have been made. Ligation of the venous return had been the subject of investigation. Brooks and his associates³⁹ had continued their work upon this subject. Although they had shown previously that ligation of the vein decreased the blood flow, results also showed a reduction in the percentage of gangrene in experimental animals. This work was extended to patients.⁴⁰ In 2 cases of localized arterial obstruction with gangrene marked improvement resulted. In 14 cases due to arteriosclerosis results were favorable in some instances but they believe that favorable results will be obtained only in a small percentage of carefully selected patients.

Suction in the treatment of peripheral vascular disease dates back many years; probably the best known work being Biers' hyperemia by suction.⁴¹ In 1933 two groups in this country, Landis and Gibbon⁴² in Philadelphia, and Herrmann and Reid^{43,44,45} in Cincinnati, independently published methods to produce changes in pressure over the extremity. Landis and Gibbon based their studies upon the sound

physical principles embodied in Poiseuille's law of the behavior of fluids in rigid tubes. Poiseuille's law states:

$$Q = \frac{\pi PR^4}{8 n L}$$

Q = volume flow per unit of time

P = pressure

R = radius of tube

n = coefficient of viscosity

L = length of tube

It can be seen from this formula that volume flow is directly proportional to the differential pressure. If, then, an artery approaches a rigid tube and one cannot increase blood flow by dilating the vessel, an increase in the differential pressure will increase the flow to the periphery. It would be possible then by increasing the differential pressure to increase the blood supply to the extremity in those cases which heretofore had been considered hopeless. Work by Landis and Gibbon upon arterial schema supported this view⁴² and experiments upon humans showed that the digital skin temperature could be raised in this way in normals and in advanced organic vascular disease.⁴⁶ Alternate suction and pressure were used with relatively brief periods of suction (−80 to −120 mm. Hg for 25 seconds) and brief periods of pressure (+60 to +80 mm. Hg for 5 seconds). Further work with this method has recently been reported.⁴⁷ Treatment is carried out for 2 hours twice daily and longer as the patient requires it. Most of the cases treated were first tried conservatively with other usual methods without benefit. The authors feel that the method is worthy of trial where ordinary means are ineffectual. Thus with help, temporarily, patients are carried over bouts of pain and ulceration, giving time for collateral circulation to develop. Results show a diminution in cyanosis, abolishment of the rest pain of ischemia, and healing of trophic ulcers. Intermittent claudication becomes milder and tolerance to exercise is increased. Contraindications to use of the method include active or spreading cellulitis and encapsulated pus in the part. Too small a number of cases have been treated to permit generalizations as yet.

The work of Herrmann and Reid^{43,45,48,49} has progressed simultaneously with, but independently from, that of Landis. They at first used negative pressure alone in cycles lasting 5 minutes, but have shortened them until at present four cycles are completed per minute. The pressure changes have been changed to −80 mm. Hg and +20 to +40 mm. Hg with 5 seconds for the positive and 10 for the negative phase. Treatment periods have been lengthened from 30 minutes to 1 to 2 hours. More recently Herrmann⁴⁹ has added 80 to 100 short oscillations per minute to the cyclic changes so that lymphatic and venous obstruction may better be treated. Herrmann and Reid have called their method Pavaex (pa-s-sive, va-seular, ex-ercise). A commercial unit is available.

The technique of alternate suction and pressure has been successful in the hands of both groups. In a recent report of Herrmann and Reid⁴⁹ results in arteriosclerosis are given. Since results seemed to depend upon the part of the arterial system affected diagnosis was extended by special procedures to localize the sites of greatest clinical importance

in each case. Seventy-five cases were divided into three groups: (1) predominant involvement of the major arteries; (2) cases with little or no knowledge of disease until trivial infection (about one-half of these were diabetics); (3) predominant involvement of the arterioles of the feet. In the first group, 10 cases, with acute or subacute thrombosis of a major peripheral artery, all had complete relief of all major symptoms. In Group 2, 46 cases (43.37%) were completely relieved, 47.83% greatly improved and 8.69% with gangrene required less radical amputations than would have been done without the treatment. In the third group, 19 cases (only 15.7%) were relieved, 42.1% were definitely improved and a like number obtained no relief.

Progress in the diagnosis and treatment of peripheral vascular disease is well summed up in the closing remarks of Reid⁵⁰ in his Matas Lecture on Vascular Surgery; "Means for estimating peripheral vascular efficiency are almost as accurate as the means of estimating the efficiency of the bloodvessels of the heart and kidney. They are waiting to be put into general use by our profession. Once it becomes the practice to study the peripheral vessels and to advise people when there is a thin margin of safety in the blood supply of their legs, there are many things that can be done to avoid those critical periods of pain, infection, gangrene and amputation. Then, too, there will be a noticeable diminution in the number of patients treated for cramps, metatarsalgia, fallen arches and rheumatism."

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(Titles have been omitted for sake of brevity.)

PEDIATRICS

UNDER THE CHARGE OF
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THE DIAGNOSIS AND TREATMENT OF PERTUSSIS.

PERTUSSIS is a disease which too often has been regarded as trivial. Parents are prone to pay little attention until the paroxysms have become severe. Even then many will manifest a philosophy of the Stoic so long as they themselves are not the sufferers knowing that in the majority of instances that a period of subsidence will develop and that sooner or later the patient will recover. On the other hand some parents will seek their physicians in an attempt to secure relief for the little patient. This is not always easy nor prompt, as experience has shown that relief is more difficult in direct ratio to the length of time that the condition has progressed. All in all whooping cough is one of the most unsatisfactory of diseases to treat. Consequently the differences of opinions of physicians in regard to the efficiency of the different therapeutic measures are as variable as the number expressing themselves. Some of the procedures used will be enumerated later and the viewpoints of certain observers will be given. From both the epidemiologic and therapeutic aspects the greatest difficulty arises from the fact that at its onset pertussis presents the same clinical picture

as acute rhinitis or acute bronchitis or the pre-eruptive stage of certain of the exanthemata. Except in the presence of an epidemic or with a history of contact with a known case, suspicion of whooping cough may not be aroused until the end of the second or the beginning of the third week, when the cough becomes more exaggerated and more paroxysmal in type. More recent efforts with the problem of pertussis have been in attempting to improve a method for earlier diagnosis and also in the development of a prophylactic material for the immunization of infants and young children. As will be shown later, encouraging results have been observed, and it is to be hoped that widespread immunization will be as successful in reducing epidemics of pertussis as it has of diphtheria.

The picture of pertussis as an acute infection with or without complications seems to be misleading according to Cockshut.¹ He suggested that pneumonia is often not a complication in the true sense, but a terminal condition. The patient may die or may recover according to the severity of the original infection, the powers of resistance of the patient and similar factors rather than to the extent and severity of the so-called complications. Whooping cough, at least in its severest form, should be regarded as an acute generalized infection. The ordinary course of the disease is one where the whoop is the dominant feature and the patient remains essentially well throughout the illness. In the severe type the patient is seriously ill from the beginning. Although the latter group requires all the benefits of therapeutic development, the milder forms also require active treatment, because even these are very distressing.

The result of vaccine treatment of pertussis has been very good in the hands of some practitioners, but in the hands of others, apparently in the majority, the results have been most disappointing. Because of this all vaccines for pertussis were omitted from New and Non-official Remedies in 1931.² In the 20 years that have elapsed since the first introduction of such a vaccine, no conclusive evidence has been accumulated regarding the therapeutic efficacy of such preparations. The Council held that it was not warranted in retaining pertussis vaccines in New and Non-official Remedies. Notwithstanding this conclusion and action these preparations in the hands of many physicians gave results that were entirely satisfactory both as prophylactic and active methods of treating this most distressing and often most dangerous disease. Bivings³ found pertussis vaccine to be an effective agent in the treatment of whooping cough and even more satisfactory as a prophylactic method. Undoubtedly he struck the keynote of the situation when he emphasized that the vaccine must be given in large doses to secure maximum results, as a few large doses were far more effective than many small ones. He rarely gave more than 4 doses, and in the few instances that he exceeded this number it was only to give 2 additional doses so that 6 doses were the greatest number of doses that were given. His procedure was to give an injection every other day beginning as soon as possible after establishing the diagnosis. In addition to giving too small doses, absence of satisfactory response has been due to the initiation of treatment being delayed until the disease has become too well developed, for the later in the course the treatment is started the more difficult it is to bring the paroxysms under control.

To avoid this in doubtful cases Bivings recommended the use of the mixed vaccine as no harmful effects ensue and in event the cough is not pertussis, immunity of several months' duration against pertussis is established. In children from 2 to 6 years he commenced with 0.5 cc. for the first dose, 1 cc. for the second, 1.5 for the third and 2 cc. for the fourth. When additional doses were given he used 2.5 cc. for the fifth and 3 cc. for the sixth doses. In the last 2 doses one-half of the quantity was injected into each arm or the entire amount between the scapulae.

Schowalter⁴ studied the statistics of 16 years from the Milwaukee County Home for Dependent Children. During the first half of this period no vaccine was used, while during the second half of the period all children under 6 years received either pertussis vaccine or pertussis ectoantigen upon admission to the institution. In this manner over 2700 children received prophylactic injections. In the first period when no vaccine was used, there was 1 year during which no cases of whooping cough developed, and another year during which the number totaled 56. The morbidity rate during this period was 67.5 per 1000 children and the mortality rate was 4.9%. During the period when the vaccine was used the morbidity rate 136.4 per 1000 children and the mortality rate was 2.9%. It is of interest to note that during the same periods in the city of Milwaukee the morbidity rates for pertussis were 255.5 and 384.7 respectively per 100,000 population, and the mortality rates were 2.8% and 0.8% respectively. Thus, while the incidence of the disease was greater during the second period, either the severity was less or treatment was of some benefit.

The therapeutics of pertussis covers a wide variation of remedies and procedures. Emetics, antispasmodic cough syrups, special preparations such as pertussin and diatussin and many other things have been used in attempts to lessen the severity of the paroxysms and to shorten the course of the disease. Ether has been recommended administered by subcutaneous injection or by rectal injection in olive oil. Wildtgrube⁵ recommended the use of a concentrated vaccine made from Bordet-Gengou bacilli given as early as possible. He commented, however, that just as good results were said to be obtained with injections of milk.

Lewis and Barenberg⁶ gave their experiences in regard to the prophylactic effect of normal whole adult blood on the course of whooping cough. Of 17 children exposed to this disease, 6 were given 30 cc. of whole adult blood and 11 served as controls. All of these children were in one ward and under the same conditions of diet, hygiene and nursing care and as all had been exposed to the same source of whooping cough, comparative results should be of considerable accuracy. All of the 6 children who received blood developed whooping cough, which, however, was of lesser severity than in the control group. Of the 6 children so treated the course of the whooping cough was mild in 5 instances and moderate in 1 case. On the other hand of the 11 untreated children, 2 had mild cases, 3 had moderate cases and 5 had severe cases. It was necessary to administer codein to 3 of the severe cases in an attempt to reduce the number and severity of the paroxysms. The authors claimed that the results following the inoculation of whole adult blood were definitely superior to those obtained with the use of pertussis vaccine. The use of the dry Lyophile serum of pooled human blood, as

developed by Flosdorf, Mudd, *et al.* and procurable at the Philadelphia Serum Exchange of the Children's Hospital, greatly simplifies the application of such treatment.

Epstein⁷ called attention to his previous report in the same periodical in 1932, in which he recommended the use of gold tribromid in the treatment of pertussis. In this later paper he reported a study and observation of 150 cases of whooping cough in children, two-thirds of whom were treated with gold tribromid and one-third, used as a control, were treated with the usual antiwhooping cough remedies. Using elixir of gold bromid in 100 children he noted that after 3 or 4 days the cough became less frequent and less distressing, the attacks were milder, the vomiting ceased and the sleep was more restful. Out of the 100 children 69 were entirely well at the end of 4 weeks, 17 at the end of 5 weeks and 14 at the end of 6 weeks of treatment. On the other hand the 50 children who were used as controls and who were treated with the usual antipertussis drugs did not fare so well. No improvement was noted until the end of the second week. Of this control series 24 were entirely well at the end of 10 weeks, 18 at the end of 13 weeks and 8 at the end of 15 weeks of treatment. The use of vaccine in 20 cases and ether in 5 did not materially influence the results.

Ellstein⁸ employed many drugs and also the vaccines with most unsatisfactory results. He treated 30 children with gold bromid and was greatly pleased with the results. In 20 cases the cough subsided in 3 weeks; in 7 cases, in 4 weeks; in 5, in 5 weeks. In all of these 30 children, after 2 or 3 days' treatment with gold tribromid, the cough was less severe, vomiting ceased and the children slept better. The dose of the Elixir Bromaurate was a teaspoonful 3 or 4 times a day after meals, or more often when necessary to control the cough paroxysms.

Barbour⁹ claimed beneficial effect in certain cases of pertussis from the administration of whole suprarenal gland. He treated 192 patients with desiccated whole suprarenal gland given by mouth at regular intervals either throughout the course of their illness or from the time he first attended them until the cough ceased. Fifty-six of the cases did so well that he used no other remedy. He found that the maximum dose required was from $\frac{1}{2}$ to 1 grain for infants and from 1 to 2 grains for children. Better results followed the administration of the suprarenal extract when given at 2 or 3-hour intervals than larger doses at longer intervals. In 38 cases thyroid extract was added. In another group of 58 cases a foreign serum protein was used. In 40 cases commercial pertussis vaccine was used with the suprarenal medication. From his observations in this study he believed that by combining the use of whole suprarenal gland by mouth and occasionally with thyroid extract and some form of serotherapy a marked decrease in the severity and duration of from 80 to 90% of the cases of whooping cough may be produced.

Weisberg¹⁰ reported a series of 116 cases of whooping cough treated with tussiva. This contains tincture of bryonia, tincture pulsatilla, eucalyptus, and golden antimony sulphid in a concentrated solution. In his routine the parents were advised in regards to hygiene and diet. His remedy was given 1 teaspoonful in about 5 ounces of water and 1 teaspoonful of this mixture was given every hour so that the patient

received 14 or 15 doses in 24 hours. Infants under 2 years of age received half doses, but occasionally it was deemed advisable to alternate a full dose. The product was readily taken and the author felt that definitely good results were produced.

In any of the many methods of treating pertussis the same handicap is encountered because of the difficulty in diagnosing this condition in the early stage except in epidemics or where there has been a known and definite exposure. A fairly early diagnosis may be made by leukocyte count. A leukocytosis associated with a persistent cough especially when showing a preponderance of lymphocytes is a fairly conclusive evidence of pertussis. The complement fixation and the agglutination tests have been used for diagnosis. Neither have been very helpful but of the two the former showed better results. An early diagnosis may be made with the cough plate method. Sauer¹¹ stated that a positive plate is indisputable evidence of pertussis, but negative plates do not exclude the disease. The same author¹² in a total of 470 cases isolated the Bordet-Gengou bacillus from 88% in the catarrhal stage, from 68% in the paroxysmal stage and from none in the stage of decline of the disease. This observation showed the value of this method in the diagnosis of this disease during the early period when ignorance of its presence and carelessness in making contacts favor the development of large epidemics. This method should be of very great value in the treatment and control of pertussis. A plate culture taken as the patient begins to show improvement will establish the time at which the patient is no longer a source of dissemination of the disease. Sauer¹³ gave in some detail the technique of preparing the culture medium and of exposing the plates, as well as the methods of incubation and interpretation of the cultures. To the general practitioner or pediatrician not having access to a properly equipped laboratory this method is of no practical value. As a refutation of the last statement Kendrick and Eldering¹⁴ described how their laboratory findings have been applied in the Grand Rapids Health department in a program of whooping-cough control. The exposure of the cough plates was done almost entirely by 25 nurses in the Bureau of Public Health Nursing. Upon the request of a physician the nurse in the particular district secured a diagnostic cough plate, and the laboratory findings were reported both to the physician and to the City Health Department. If the first plate was negative or unsatisfactory and the diagnosis of whooping cough had not been ruled out in the meantime, a second plate was obtained. While only 22 physicians availed themselves of this service during the first year, there were 70 users during the second year. Another phase of this method according to the authors is its use in releasing from quarantine restrictions cases which have become negative bacteriologically as was mentioned previously.

City, State and Federal reports show that whooping cough differs from other contagious diseases in that nearly all of the deaths occur before the third year of life. Whooping cough is relatively benign after infancy. This epidemiologic fact emphasizes the urgency for attempts at eradication of the disease during the early years of life and warrants an immunization especially of infants and children less than 3 years of age. The *Bacillus pertussis* vaccine used now over a period of 5½ years differs from other vaccines used for pertussis. In

addition to the older forms of Bordet-Gengou bacillus it contains recently isolated, hemolytic strains of the Bordet-Gengou organism and the preparation is made freshly every few months. Another very important point is that the medium used in its culture contains 20% of freshly defibrinated human blood. Sauer¹⁵ described how the 48-hour growth is scraped off and suspended in physiologic solution of sodium chlorid, containing 0.5% of phenol. After a week the pure, sterile vaccine is diluted to contain 10 billion bacilli per cc. About 650 non-immune infants were given the vaccine before any exposure had occurred. The total dosage after 6 months of age was 8 cc. In administering the vaccine 1 cc. is injected just under the skin in the deltoid region of each arm. One week later 1.5 cc. are injected under the skin in the biceps region of each arm. After another interval of 1 week 1.5 cc. are injected in the triceps region of each arm. The youngest group of children to whom vaccine was administered consisted of 150 infants less than 3 months of age. Each of these were given a total of 6 cc. Their local and systemic reactions were negligible. The age of the main group of non-immune children who received injections in this series of Sauer, numbering more than 500, ranged in age from 6 months to 4 years, the average age being 14 months. Taking all factors into consideration the best age for immunization is between the seventh and the tenth months. In giving the injection the skin should be cleansed with alcohol and the syringe and needle should be sterilized thoroughly by boiling. Reactions to the injections are chiefly local, although transient rise of temperature may occur in from 4 to 36 hours after an injection. The reactions are due to the bacilli and their products both toxin and endotoxin. The cloudiness of the vaccine is due to the bacilli. The special nature of the suspension is a factor in the slow absorption. A transient local redness, tenderness and induration may be noted in some instances. No reaction in this series was severe enough to necessitate the postponement of the subsequent injection. More than 3500 injections were given without the occurrence of infection at the site of the injection. Each mother was told, just before and after the first injection and after the subsequent injections, that if a local reaction or tenderness should develop she should not be concerned. Local reactions usually reached their peak about 24 hours after the injection, after which the tenderness rapidly subsided. At the time of the subsequent injections a small, circumscribed residual induration of the skin or a subcutaneous nodule might be felt. The persistence of these small nodules was probably due to the slow absorption which results from the toxic action of the vaccine on the subcutaneous tissues. This vaccine contains no foreign serum and will not sensitize, nor will it cause anaphylactic reactions, serum sickness or the phenomenon of Arthus. The active immunity conferred by the vaccine seemed to depend on the potency and the interval of time between injection and exposure. This period should be at least 4 months. Adherence to the technique of administration is of the utmost importance. In this paper Sauer makes no claims for this material as an active therapeutic agent in the developed disease. However, bacteriologic houses are now selling a preparation containing the hemolytic pertussis organism which they recommend for the treatment of the active disease.

Although Sauer seems to have published more papers on this treat-

ment than any other one person, credit for its development belongs to Krueger. The manufacturers call this new preparation Sauer's vaccine yet Frawley, Stallings and Nichols¹⁶ stated that Krueger and Krueger, Nichols and Frawley had recently described a method for the preparation of a new pertussis antigen. This method of antigen production by endotoxin-producing cells such as streptococci, gonococci and *Bacilli coli* had previously been developed by Krueger. The essential feature of this process is the physical disruption of the living cells with the extraction of the endocellular elements without the use of heat or chemicals and thereby obviating denaturation reactions. In Germany the new, toxin-free vaccine for whooping cough is called "Petein." According to Krueger¹⁷ this was developed by H. Langer from 58 strains of *B. Bordet-Gengou* of the hemophilus type. In its preparation the greatest care is taken in preserving the presence of a high quota of blood in the medium, and to remove the endotoxin from the bacterial bodies, because of the fact peculiar to whooping cough, it is not the endotoxin that releases the toxin-antitoxin effect, but it is the bacterial bodies that stimulates the formation of the antibodies.

Frawley¹⁸ discussed the results of 2 years' experience in the prophylactic treatment of pertussis. Because of the absence of reactions it is possible to carry out a vaccination program on large groups of children entering school life. Such children are especially in need of prophylactic vaccination as they are at this time most likely to be thrown in contact with the disease. This is much the worst age for contacts, although the infants show a much more serious illness from the disease. Infants are less exposed to pertussis and usually then through older children of the family making contact in school. From the standpoint of preventing epidemics immunization of kindergarten and preschool children is of the utmost importance.

In the treatment of the active case of pertussis several criteria enter into the evaluation of inoculations. The first of these in importance is the quality of the vaccine. The second is the time at which treatment is started and the third is the suggestive component. If inoculation in the organic or infectious stage of the disease in infants or in non-suggestible children stops the vomiting, improves the appetite, reduces the number and the severity of the attacks especially the whoop, and finally checks all coughing within a reasonable time, a specific effect must be granted. Rosenbusch¹⁹ recommended the use of vaccine although his observations were not made with the new vaccine which contains the *Hemophilus pertussis*. Gundel²⁰ stated that the so-called polyvalent whooping-cough vaccines heretofore available were mostly non-specific vaccines, consisting for the greater part of *B. influenza*. He felt that the new development containing *Hemophilus pertussis* promises to be of great value in the treatment of the active disease in addition to its value as a prophylactic agent.

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PHYSIOLOGY

PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 20, 1935

Platelets and the Structure of the Blood Fibrin Gel. L. M. TOCANTINS (Department of Medicine, Jefferson Medical College). Platelet-free clots show less rigidity, firmness and contractility than platelet-rich clots. Observations on platelet-rich and platelet-free recalcified oxalated and citrated plasma, heparinized plasma, thrombopenic and hemophilic plasma undergoing coagulation under the microscope, led to the following results and interpretation of the relation of the platelets to the structure and physical properties of the blood gel:

Soon after the fibrin is laid down, intact platelets in the interior of the clot converge toward the fibrin threads, adhere to them, and form firm knots at their intersections. As these knots are formed the threads

become bent, twisted and shortened. By contrast, in platelet-free clots or platelet-rich clots to which antiplatelet serum has been added, the threads are rarely united and remain straight and tense for a long time.

It appears that it is by binding the fibrin threads together at their intersections that the platelets render the clot firm, rigid and elastic. It is perhaps while this is taking place and as a result of it that the clot undergoes the visible reduction in volume (syneresis).

Fibrin does not issue from platelet clumps as generally contended; these clumps form around the previously laid fibrin.

Observations on the Variation of the Diphtheria Bacillus. H. E. MORTON (Laboratory of Bacteriology, University of Pennsylvania). In a study of the diphtheria bacillus from the standpoint of variation, at least four stable colony types were found. By applying the present bacteriologic nomenclature to the colony types, we have the smooth (S), intermediate (SR), rough (R) and dwarf (D) types of diphtheria colonies. A comparative study of these colonial types has shown that many of the heretofore described discrepancies in the behavior of the diphtheria bacillus can be correlated with colony form. It is the SR type which is most frequently encountered and which appears to be the most pathogenic. The S, R and D types are less pathogenic, but not totally avirulent. The SR type shows the characteristic irregularly shaped and unevenly staining cells. The S type shows more regularly shaped and more evenly staining forms. The R type shows more solid staining, shorter and thicker cells and a tendency for the cells to remain attached to one another. Organisms in the D type of colonies are very minute rods. S and D forms give stable suspensions in physiologic saline solution, the R type clumps spontaneously, and the SR type gives intermediate reactions. All types give the same fermentation reactions, there being, however, some quantitative variations. In general, the various colony types show quantitative rather than qualitative variations in the various tests to which they were subjected.

Relation Between Intracellular Acidity and Roentgen Ray Sensitivity. R. E. ZIRKLE (Johnson Foundation, University of Pennsylvania). The Roentgen ray sensitivity of *Paramœcium* and of the spore of the fern *Pteris longifolia* is markedly altered by the presence of penetrating acids and bases during irradiation. In the fern spore, increase in concentration of carbon dioxid or hydrogen sulphid first increases and then decreases the radiosensitivity, the range of variation being greater than 1 to 2. Increase in concentration of ammonia first decreases the sensitivity and then increases it. These changes all occur with concentrations that have no effect in absence of Roentgen rays. The sensitivity of *Paramœcium* is similarly altered, except that smaller concentrations are effective and the effect is complicated by the onset of toxicity of the penetrating acids and bases themselves.

In the fern spore the quantitative relations between intracellular acidity and radiosensitivity are markedly dependent upon the intensity of the Roentgen rays.

Studies on Osmotic Equilibrium and on the Kinetics of Osmosis in Living Cells by a Diffraction Method. BALDUIN LUCKÉ, MARTIN G. LARRABEE and H. KEFFER HARTLINE (Laboratory of Pathology and

Johnson Foundation, University of Pennsylvania). Osmotic equilibrium and kinetics of osmosis of living cells (unfertilized eggs of *Arbacia punctulata*) have been studied by a diffraction method. This method consists in illuminating a suspension of cells by parallel monochromatic light and measuring, by means of telescope and scale, the angular dimensions of the resulting diffraction pattern from which the average volume of the cells may be computed. The method is far less laborious and possesses several advantages over direct measurement of individual cells. The average size of a large number of cells is obtained from a single measurement of the diffraction pattern and thus individual variability is averaged out. The observations can be made at intervals of a few seconds, permitting changes in volume to be followed satisfactorily. During the measurements the cells are in suspension and are constantly stirred. Volumes of cells in equilibrium with solutions of different osmotic pressure have been determined. In agreement with our previous experiments, based upon direct microscope measurements, we have confirmed the applicability of the law of Boyle-van't Hoff to these cells; that is to say, the product of volume and pressure has been found to be approximately constant if allowance be made for the volume of osmotically inactive material of the cell contents. The volume of osmotically inactive material was found to be, on the average, 12% of the initial cell volume; in eggs from different animals this value ranged from 7 to 20%. Permeability to water of the *Arbacia* egg has been found to average at 22° C. 0.106 micron of water per square micron of cell surface, per minute, per atmosphere of difference in osmotic pressure. Permeability to ethylene glycol has been found to average, at 24° C., 4×10^{-15} molecules, per square micron of cell surface, per minute, for a concentration difference of 1 molecule per liter. This is in agreement with the values reported by Stewart and Jacobs.

Studies on the Identification of a Compound Isolated From Scallop Muscle. ELINOR MOORE and D. WRIGHT WILSON (Laboratory of Physiological Chemistry, University of Pennsylvania). Guanidin compounds have long been known as constituents of muscle extracts. Within the past few years two of these, creatin and arginin, have been shown to be present as labile phosphoric acid compounds which are of great importance in muscle metabolism. Recently several invertebrates have yielded guanidin derivatives of unexpected nature. It is, therefore, of interest to find still another member of the series in a compound isolated from the extract of the adductor of the deep-sea scallop.

Analysis of the picrate of this substance for carbon, hydrogen and nitrogen, the only elements present besides oxygen, points to the formula $C_9H_{18}N_4O_4$ for the free compound. The molecular weight found is 240, which agrees with 246 calculated from the formula. Tests and analytical results show the absence of rings. There is no primary amino group, no ordinary peptid bond and no N-alkyl group. The four oxygens are thought to be in two carboxyl groups, one of which is titrated in alcohol. There must be an asymmetric carbon. The presence of a monosubstituted guanidin group is indicated by the acetyl-benzoyl and Sakaguchi reactions and by the splitting off of urea

with barium hydroxid. The monoprimary amin, $C_8H_{16}N_2O_4$, formed by this treatment, yields on oxidation with silver oxid nearly two equivalents of carbon dioxid and one of ammonia and also acetaldehyd, acetic acid and an amin as yet unidentified.

It is tentatively suggested that the compound may be a derivative of arginin, formed by substitution on the α -amino group with propionic acid attached through the α carbon.

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AUGUST, 1935

ORIGINAL ARTICLES.

THE PITUITARY IN EXPERIMENTAL CRETINISM.

I. STRUCTURAL CHANGES IN THE PITUITARIES OF
THYROIDECTOMIZED RATS.*†

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VERY little attention has been paid to the histologic changes in the pituitary in hypothyroidism. The studies which have been published (chiefly in the German literature) show great variation in statement of observations and no agreement in interpretations of these observations. These discrepancies are probably due partly to confusion between acidophils and basophils, which Bailey and Davidoff² and Biedermann³ have shown may easily occur by various staining techniques, and due partly to previous lack of knowledge of the facts that are now established concerning the concrete functions of the pituitary cells. The present study was made with the view of studying the pituitary after thyroidectomy in the light of our recently acquired knowledge of the definite thyroid-pituitary relationship.

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At present the growth hormone of the pituitary is attributed to the acidophil (or eosinophil) cells which in the rat constitute roughly 32% of the cells, and the gonadotropic hormones to the basophil cells which constitute about 15% of the cells.¹⁵ The acidophils and basophils are called chromophils because their granules take up dyes. The poorly staining chromophobes or chief cells, whose activities are unknown, make up the remaining 53% of the cells. Severinghaus¹⁵ gives a good discussion of the various points of view concerning possible transitions of one cell type to another.

The existence of thyrotropic hormone has been demonstrated by pituitary implants and extracts, which produce definite structural changes of hyperplasia in the thyroid and raise the basal metabolic rate, the guinea pig being particularly sensitive for its demonstration. No one has so far ventured to ascribe the production of this hormone to any of the cell types in the pituitary. Removal of the pituitary results in atrophy of the thyroid and decreased basal metabolic rate which is ascribed to absence of the thyrotropic hormone.

The present paper is concerned with the structural changes in the pituitary resulting from the loss of thyroid secretion.

Experimental Methods. The white rats used were in most instances litter mates, in a few cases rats of the same age but of different litters. Thyroids were removed under ether anesthesia, avoiding the parathyroids, and growth curves plotted thereafter. The operation was carried out at ages varying from 24 to 69 days (average 41 days). The stunting of growth was taken as the criterion for adequate thyroidectomy. Some cretins and controls were kept in the same cage, so as to maintain the same conditions of food and environment; other cretins were kept in a cage alone so as to be spared the competition of the larger, more active controls. A few animals died spontaneously at early periods after operation, perhaps of parathyroid tetany, with no discovered anatomic lesions except those in the pituitary; and, as their pituitaries differed in no way from those of rats intentionally sacrificed, their pituitaries are included in the present series. All of the long-time cretins were killed with chloroform when in good condition, at the time interval desired up to 10 months after operation. Thirteen male cretins were studied (of these 4 died spontaneously), 12 female cretins (of these 3 died spontaneously), 3 rats thyroidectomized when adult, and 28 normal controls.

Pituitaries were weighed and then fixed in Helly's fluid. Serial sections were made at first, but it was found that the changes occurred quite uniformly throughout the pituitary, so that sections made from four different levels of each pituitary were adequate. Frequently control and cretin pituitary were mounted on the same slide so that both were subjected to identical staining conditions. The slides were stained with 10% acid fuchsin, rinsed in water, then stained with Mallory's aniline blue orange G mixture and then rapidly dehydrated in 95% and absolute alcohol. Hematoxylin and eosin staining is of little value, as basophils are not stained properly and a hyalin material stored within the cells stains pink and is indistinguishable from cell cytoplasm and granules. Giemsa staining was not found suitable. Various staining methods advocated for pituitary using acid violet were not found to give satisfactory staining for basophils in our hands. Formalin fixation gave poor results.

RESULTS. *Histologic Changes in the Pituitary.* Thyroidectomy performed in young rats results in the following characteristic sequence of changes in the anterior lobe. At the end of 7 and 9 days (Rats 3 O 8, 2 O 1, 4 J 7) there was no definite change. At 11 days Rat 2 O 2 showed increase in the number of large blue granular cells with accentuated outlines indistinguishable from the normal cells designated basophils.

By the 14th and 18th day (Rats T 1, 2 J 2) these basophilic elements were greatly increased in size and number (Fig. 2). In a few cells there appeared a definite vacuolization, and some were so full of fine vacuoles as to appear foamy. Occasionally there appeared to be a coalescence of smaller vacuoles to form larger ones. Many cells showed masses of a pale blue, homogeneous, hyalin material, in which empty vacuoles often occurred. The acidophils were distinctly decreased in numbers and in those that remained the granules were fading away so that it became very difficult to distinguish them from chromophobes.

By the 29th day (Fig. 3) in Rats O 5, R 8, R 4, most of the acidophils had disappeared. The majority of cells were altered cells with granules which stained indefinitely or distinctly blue, and these cells contained a large amount of hyalin material which often coalesced to form single globules of large size which almost completely filled the cells, pressing the nucleus to one side, while there still remained an equal number of finely vacuolated cells which did not contain hyalin material but rather a finely granular precipitate or remains of granular cytoplasm in an otherwise empty space. All intermediate stages between these two conditions were seen. Much less than half of the cells seen in the slide were chromophobes. No difference in fat content could be detected histologically in pituitaries 21 and 26 days after thyroidectomy (Rats 2 U 4, 2 U 2, 3 N 5).

At 33 and 35 days two rats (3 M 7, 3 G) showed the majority of cells to be large basophils. Where hyalin material occurred it was seen to be in basic staining cells.

At 37 days, in a very much dwarfed rat (R 5), the pituitary presented an astonishing picture (Fig. 4). Most of the cells were enormously altered. The transition was still more complete toward cells containing dense blue hyalin material, while some still showed fine coalescing empty foamy vacuoles. Only on close examination could basophils without vacuoles or hyalin material and chromophobes be identified. Very few acidophils could be found.

By the 48th day (Rat 2 N 1) the fine foamy vacuoles had nearly disappeared, and the cells had more the character of "castration cells," containing large homogeneous blue hyalin material, displacing the nucleus and cytoplasmic granules to one side. The hyalin varied in staining reaction, some appearing pale, some dark blue.

At 56 days, Rat 4 J 4 showed much the same appearance.

At 71 days (Rats 3 M 2, 3 B 4) the majority of cells had somewhat the "castration cell" appearance. Sometimes masses of cell granules were caught in the hyalin material, but usually cell granules were displaced to one margin of the cell (Fig. 5). The hyalin material became more dense and stained more deeply as time elapsed after thyroidectomy. Very few acidophils could be identified in Rat 3 M 2.

At 88 days Rat 3 H 2, which had been stunted in growth but which had started to grow again, and at 109 days Rat 3 D 1 and at 110 days Rat 3 A 3, which had never been dwarfed, were found to have thyroidectomy cells but showed the presence of many acidophils. Presumably a fragment of remaining thyroid had regenerated. These observations support the view that will be considered later, that the stunting of growth in the cretin is due to loss of acidophils. Acidophils were only found in considerable numbers in cretins when there was resumption of growth.

At 100 days in one rat (3 K 6) qualitatively the same changes were found as at 71 days but there seemed to be fewer thyroidectomy cells and more chromophobes. Again very few acidophils could be found.

One rat (3 J 6) was a cretin female which had been mated with a cretin male and gave birth to a healthy litter of young. She was killed 29 days later, 121 days after thyroidectomy. The pituitary showed the same changes (Fig. 6), in which the thyroidectomy cells resembled somewhat the so-called "castration cells;" but there were many acidophils in this pituitary. Had the fetal thyroid restored to a certain extent the maternal pituitary?

At 292 days Rat 2 V 2 showed considerable condensation of hyalin material and very few acidophils. There were more chromophobes than "thyroidectomy cells" at this stage.

No histologic differences in reaction of the pituitary could be detected between male and female rats.

Two rats (3 A 4, 3 A 5) that had been thyroidectomized when young but had never been stunted in growth were killed 110 and 124 days after operation. Their pituitaries showed abundant acidophils. No conspicuous vacuolation or hyalin material was present. Although no thyroid was found grossly at autopsy, presumably a slight amount was present which permitted body growth and prevented extensive changes in the pituitary. Apparently thyroidectomy (including aberrant thyroid tissue) must be complete, before extensive changes occur in the pituitary.

Only a few adult rats were thyroidectomized. In the young rats, the stunting of growth is proof of adequate thyroidectomy. In the adult rats this proof of adequate operation is out of question. Since we are at present interested in cretinism rather than adult myxedema we have not attempted the tedious and difficult procedures of basal metabolic rate determinations or serial sections of neck organs in

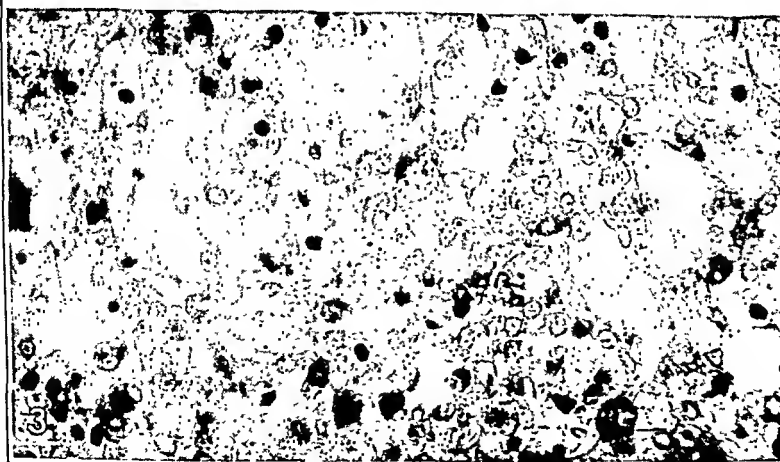
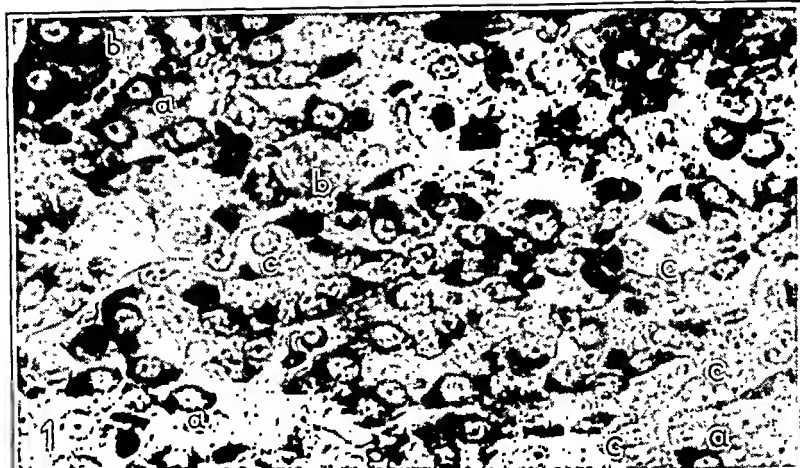


FIG. 1.—Normal rat pituitary—R 9, as a standard of comparison for the subsequent illustrations. In a black and white photograph it is difficult to appreciate the distinction in cell types which are obvious in the stained section. The small dark cells (a) are acidophils, the large dark cells (b) are basophils, and the indefinite cells (c) are chromophobes. (Approximately $\times 566$.)

FIG. 2.—Rat T 1 killed 14 days after thyroidectomy, showing prominent basophils which are increased in number and size. ($\times 482$.)

FIG. 3.—Rat R 4 dying spontaneously 29 days after thyroidectomy. Vacuolization is advanced, and extensive deposition of hyalin material is seen. ($\times 482$.)

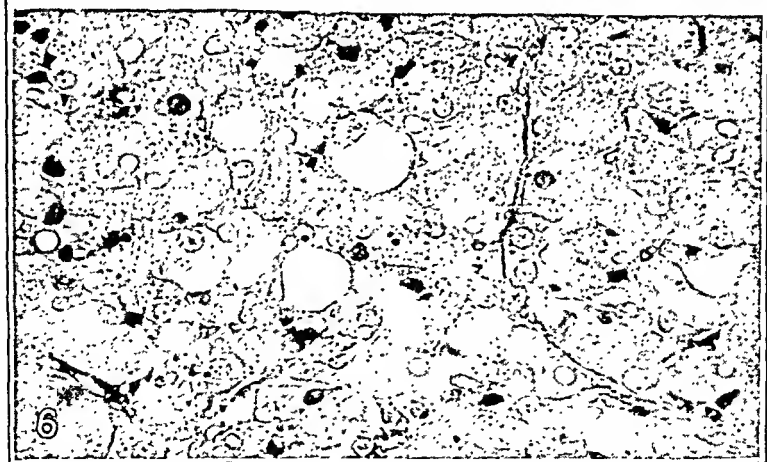
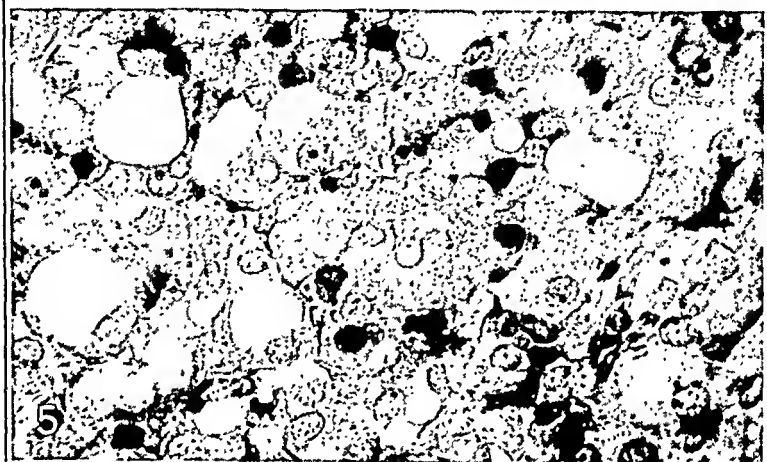
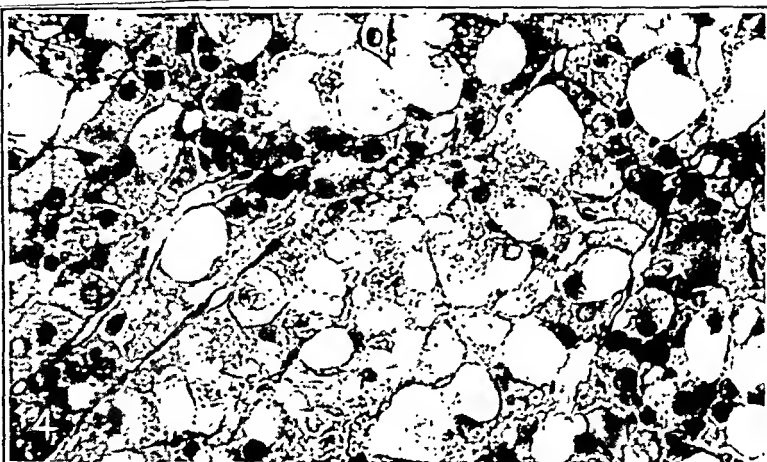


FIG. 4.—Rat R 5, markedly dwarfed and sluggish, was killed 37 days after thyroidectomy. The majority of cells contains a large amount of hyalin material which sometimes stains pale blue, sometimes darker blue. Many small, empty vacuoles are seen in cells, sometimes in the midst of hyalin material. Cell granules are seen in many cells in between vacuoles and sometimes in the midst of hyalin material. Acidophils have largely disappeared. (Ca. $\times 482$.)

FIG. 5.—Rat 3 B 4, thyroidectomized at 161 days of age, and killed 71 days later. Hyalin material occurs in single dense globules within cells showing basic granules. Hyalin material varies greatly in intensity of staining. ($\times 566$.)

FIG. 6.—Rat 3 J 6, killed 121 days after thyroidectomy. This rat had given birth to a litter of young 29 days before. "Thyroidectomy cells" bear some similarity to "castration cells." More acidophils were present in this pituitary than is usual in cretin pituitaries. ($\times 523$.)

order to prove adequate thyroidectomy in the adult animals. However, granting these qualifications, it may be stated that 3 adult thyroidectomized rats have shown marked vacuolization of basophilic cells and hyalin deposit and reduction in number of acidophils (Fig. 5).

Pituitary Weights. It is repeatedly stated in the literature that the pituitary is increased in weight in cretin animals. We were interested in determining whether this increase was due to cellular or fluid increase. We also wished to see whether the cretin's pituitary was increased in weight above that of rats which were of the same body weight as the cretin but of a younger age.

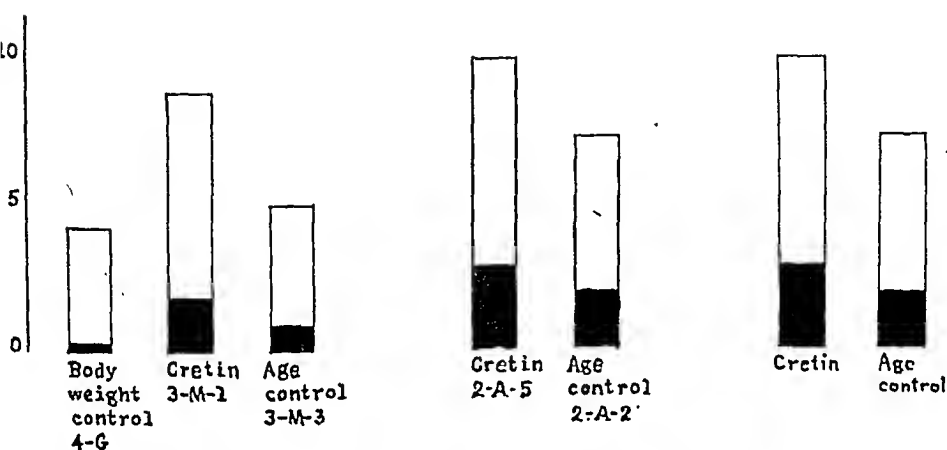


CHART I.—Fluid and solids in pituitaries of cretins and controls. The dark blocks indicate dry weights of the pituitaries, the height of the entire column the weight of the fresh pituitary before it was dried. The white block or difference between wet and dry weights represents fluid in fresh pituitary.

The pituitaries of several rats were weighed as soon as removed, dried in an oven at about 60° C. until the weights were constant, and left in a desiccator and weighed again. The difference between original and final weights represented fluid in the original gland. Chart I shows the results in 3 cretins with age controls and one body weight control. It will be seen that the cretin pituitary has a real increase in solid as well as in fluid.

Often the actual weight of the cretin pituitary is greater than that of the control rat, but sometimes there is only an increase in the percentage weight of the cretin pituitary (% of body weight).

When the weight of the pituitary is calculated in ratio to body weight of the rat and this value compared in the cretin with its age control, the degree of hypertrophy in the cretin reaches its maximum quite soon (Chart II).

When the actual weight of the pituitary, rather than its relation to body weight, is charted, and the cretin compared with rats of

similar body weight but younger rather than with rats of the same age (Charts III and IV), it is found that in the male the pituitary tends to be heavier than that of the normal rat of the same body weight, but that in the female there is some variation to this rule, probably because the pituitary in the female goes through cyclic changes in estrus.

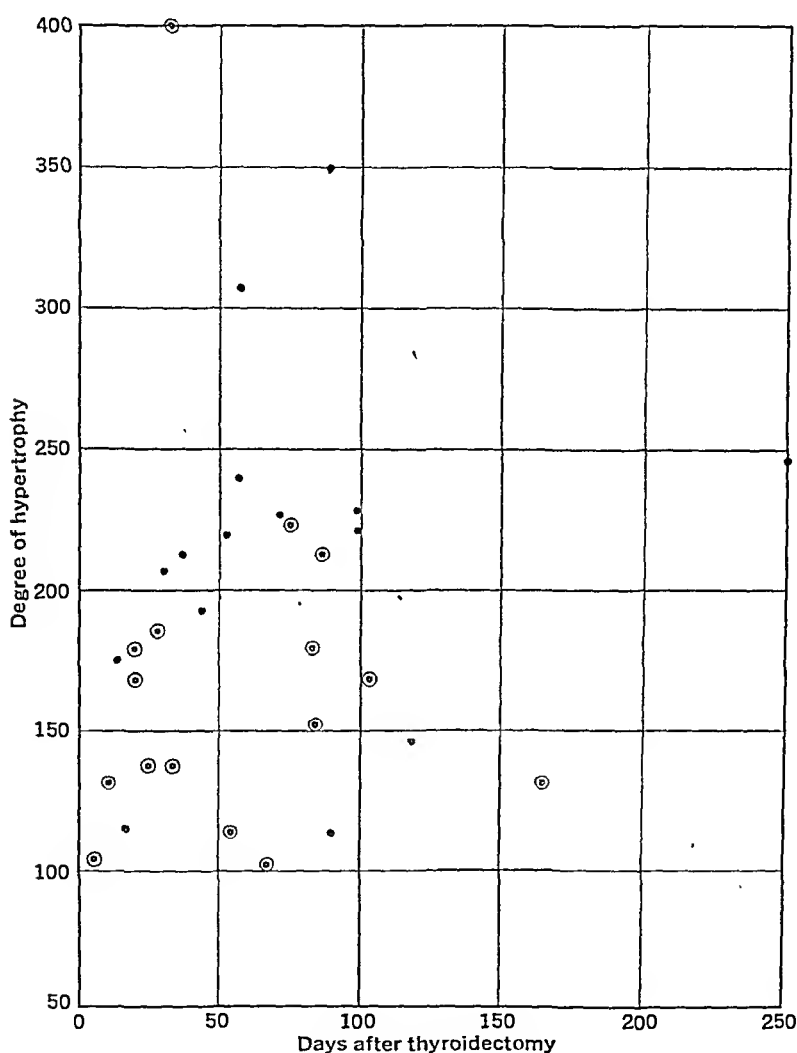


CHART II.—Degree of hypertrophy is expressed as

$$\frac{\% \text{ weight of pituitary of cretin}}{\% \text{ weight of pituitary of age control}} \times 100$$

 ○ Females.
 ● Males.

Discussion. It is accepted that there are more pituitary hormones than there are histologic cell types in the pituitary. Presumably, therefore, cells of a given histologic type, such as the basophils, may elaborate more than one hormone, just as the simple acinar cells

of the pancreas elaborate several different enzymes. After thyroidectomy there is no question of the great increase in basophils, which to all appearances, when studied at varying time intervals, are the cells which develop the striking vacuoles and hyalin deposits. As time increases and the hyalin material becomes condensed in

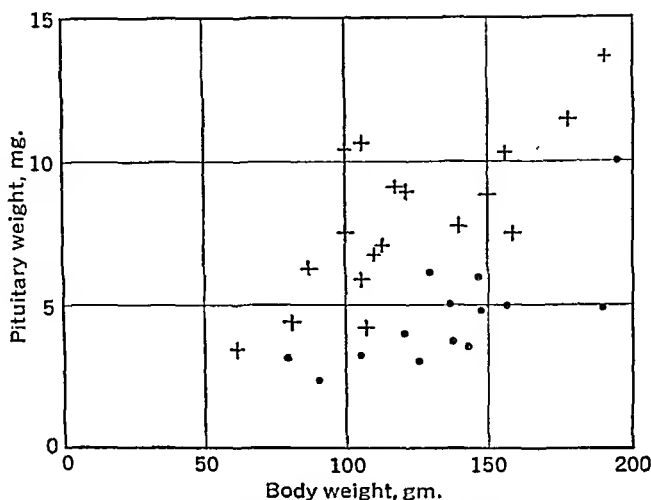


CHART III.—Pituitary weights plotted against body weights in male rats.
+ Indicates cretins; • indicates normal rats.

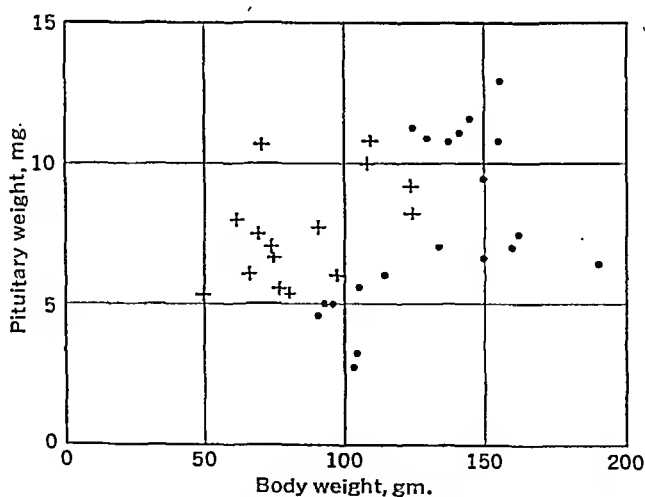


CHART IV.—Pituitary weights plotted against body weights in female rats.
+ Indicates cretins; • indicates normal rats.

single globules these cells come more and more to resemble the histologic appearance of "castration cells."

The first point for consideration in the interpretation of the "thyroidectomy cells" is whether they represent degenerative changes or secretory phenomena. Staining for fat revealed no

fatty degeneration. Moreover, the histologic appearance strongly suggests secretion if we compare them with the "castration cells" which have repeatedly been accepted as representing secretion. In work in progress it appears that pituitaries of cretin rats contain an abundance of thyrotropic hormone and this may represent an excess of thyrotropic hormone, if it is considered as the amount of hormone available per unit body weight of rat. The quantitative data will be given in a subsequent paper. From this result we feel justified in regarding much of the hyalin material as possibly accumulations of thyrotropic secretion, just as the hyalin material seen in castration cells of the pituitary has been shown by implantation experiments to represent an excess of gonadotropic hormones. This secretion of thyrotropic hormone in a hypothyroid animal seems reasonable in view of what is known of the physiologic principles of reciprocal relations between organs by which there is maintained a condition of equilibrium or "homeostasis" (Cannon⁶). When there is a lack of thyroid secretion therefore, it is possible that there should be a compensatory hypertrophy of those pituitary cells which form thyroid stimulating hormone, which would act upon any remnant of thyroid tissue that was present. Or the deposition of hyalin may indicate storage of thyrotropic hormone for which there is no utilization in the absence of the thyroid. In the normal rat pituitary isolated basophilic cells can be found containing hyalin material and this has been considered to be secretion of some sort. The "thyroidectomy cells" manifest this normal secretory appearance carried to great excess.

The histologic evidences of secretion and storage in cretin pituitaries seem greater than any changes in thyrotropic hormone content that was found on implantation of the pituitaries. The question therefore arises as to whether these cells are secreting and storing other hormones in excess. It soon became apparent that there were alterations in the weights of the adrenals and gonads in cretin rats, which suggested that there might be alterations in adrenaltropic hormone and gonadotropic hormone content of cretin pituitaries. Such studies are now in progress.

Morphologically there are distinct differences between the changes in the pituitary resulting from thyroidectomy and those resulting from castration. It is only at long intervals after thyroidectomy that the cells are somewhat similar to castration cells. The intracellular globules of "castration cells" are large, smooth, well defined, appear to be composed of dense secretion, hyalin in appearance when fixed and stained, and push to one side the basophilic granules in the cell, but in thyroidectomy cells the secretory accumulation has a less regular contour (Fig. 5). We have not seen in early stages of "castration cells" the characteristics observed in early stages of "thyroidectomy cells." In both cases, thyroidectomy and castration, there is preliminary to the formation of vacuoles a distinct

increase in large solid basophilic cells. In the castration pituitary, acidophils are abundant, in the thyroidectomized rat, acidophils are strikingly reduced.

The increased weight of the pituitary in proportion to body weight, and the fact that this increase is not due merely to increased fluid content, tends to indicate that this is not a degenerative change. It might be due to cellular hyperplasia or to increased content of a secretion which contains solids. It is apparent microscopically that there is at least a relative increase of cells of basic staining, and of chromophobes. Also, since the acidophils have largely disappeared and the pituitary is increased in weight, this increase in non-acidophil cells probably represents an absolute as well as relative increase of this cell type. The changed proportion in cell types suggests the probability of a corresponding change in proportion of hormones produced.

Another point for discussion is the disappearance of acidophil cells. This cannot be a matter of pressure atrophy, for in the castrate pituitary the basophilic hyperplasia is excessive and the entire gland is much enlarged, and yet the acidophil cells remain. After thyroidectomy, some regressive changes are seen in acidophils but these are not obvious. There seems to be a fading away of granules, in other words, a dedifferentiation of the cell, perhaps a reversion to the chromophobe type. The vacuolated and hyalin-containing cells show granules which are basophilic and there is no evidence that the acidophil passes directly to the vacuolated cell. Rather do the vacuoles seem to be a gradual change occurring in cells of indefinite or of basic staining. One point is definite: Since there is extensive disappearance of acidophils in the cretin pituitary, these cells cannot be the ones which produce the thyrotropic hormone, which is definitely present in large amounts in cretin pituitaries. This finding, we maintain, refutes the suggestion of Marine, Rosen, and Spark, who suggest that "the acidophilic granules contain the thyrotropic factor." Their statements, it should be noted, are based only upon histologic studies of the pituitary under various experimental conditions and not upon assay of pituitary potencies by implantation, such as we have carried out.

A point to be emphasized is that the stunting of growth of the cretin appears to be due to the extensive loss of acidophils. As far as we know, such an explanation for cretin dwarfism has not been stated in the literature. The reduction in numbers of acidophils has been reported in the literature, but attention does not seem to have been drawn to the relation of this to cretin dwarfism. It seems apparent from these experiments that the stunting of growth in the cretin has its immediate cause in the failure of the pituitary to produce growth hormone because of loss of acidophils which in turn is due in some way to the loss of thyroid secretion. Only in animals which are not stunted in growth did acidophils appear in

considerable numbers. The skeletal changes are different, to be sure, in cretinism and in pure hypophyseal dwarfism; but though qualitatively different, it is easily possible that the failure to obtain normal size is due to loss of acidophils in both instances. The association of acidophilic tumors or acidophilic hyperplasia with acromegaly has been taken as good evidence that the growth hormone is produced by acidophils. The reduction in acidophils in cretin dwarfism is another bit of evidence of a different type supporting the view that growth hormone is produced by acidophils.

Experiments are now in progress to determine whether the administration of thyroid extract will restore the structure of the cretin pituitary to normal.

It is a difficult matter to determine the origin of the "thyroidectomy cells." These cells must arise either as an alteration of one of the three standard types of cell or from a cell heretofore not recognized as an entity. We do not venture to postulate the latter. The vacuolation and hyalin deposition is preceded by distinct increase in numbers of basic staining cells which we cannot differentiate from the usual basophils. The dedifferentiation and then complete disappearance of acidophils concomitant with the rise in these thyroidectomy cells strongly suggest that the acidophils are the original source of the thyroidectomy cells; that perhaps they first become chromophobic in nature by loss of specific granules and then differentiate toward the basophil type. However, this is mere speculation, and an origin from newly formed basophils cannot be excluded. The absence of frank degenerative changes in the acidophils in the early stages when some are present suggests that they have become transformed in character rather than that they have been lost by atrophy and disintegration.

Previous Studies. Trautman¹⁸ in a lengthy article reviews extensively the literature on pituitary changes after thyroidectomy up to 1916. From the more recent literature, as from the older, it is evident that there has been a lack of agreement as to which histologic type of cell is involved in the vacuolation, and whether this vacuolation is a retrogressive degenerative change or a hypersecretion. Only occasional studies, as that of Hohlweg and Junkmann,⁷ and of Severinghaus, Smelser and Clark,¹⁶ have been made in the light of our recent knowledge of the thyrotropic hormone. As examples of some of the differences of opinion may be cited the following:

The early German studies of the histology of the pituitary in human and experimental hypothyroidism were initiated by the idea that the pituitary and thyroid were similar histologically and functionally and that the pituitary probably showed compensatory hypersecretion in the absence of the thyroid. Rogowitsch,¹² in 1889, found that the pituitary of rabbits 1 to 10 weeks after thyroidectomy showed cells of increased volume with vacuoles, and colloid

material in the ground substance. He noted only slight changes in the chromophils. He interpreted the changes as both degenerative and hypersecretory. Stieda¹⁷ in 7 thyroidectomized rabbits 1 to 12 weeks after operation saw no degeneration and no hyperplasia but a hypertrophy of the chief cells which showed vacuolization. He believed the changes were due to hyperactivity. He noted no changes in chromophils. Herring⁵ found no changes in the anterior lobe of 3 thyroidectomized rabbits. Kojima⁸ noted in thyroidectomized rats many large cells with vacuoles and hyalin substance. Ordinary "oxiphils" and "basiphils" were few. Poos¹¹ (extensive bibliography) found in thyroidectomized dogs and cats the appearance of a new cell as the chromophobes disappeared. These thyroidectomy cells he regarded as identical with "Schwangerschaftszellen" (pregnancy cells) and with castration cells. He stated that the eosinophils increased relatively and absolutely and he regarded this as an expression of hyperfunction. He found young animals reacted less than did old ones. Hohlweg and Junkmann⁷ found after thyroidectomy of young rats the disappearance of acidophils and the appearance of vacuolated cells which looked like castration cells but which proved to be different when the gonadotropic potency of the pituitaries was tested. They also stated that cretin pituitaries showed no increased thyrotropic effect when injected into guinea pigs, but studied intervals after thyroidectomy up to only 20 days. Bryant⁴ found in thyroidectomized rabbits a disappearance of acidophils and hypertrophy of chromophobes with later vacuolization and disintegration. He believed there must be decreased secretory function. Severinghaus, Smelser, and Clark¹⁶ have recently described the changes in 9 thyroidectomized rats as "typical castration cells" with degeneration of acidophils and appearance of nuclear inclusions. Marine, Rosen, and Spark¹⁰ have just published histologic studies on goitrous and on thyroidectomized rabbits. They found pituitary hypertrophy, and disappearance of acidophils, which they attribute to degranulation, but do not mention basophils or vacuolated "thyroidectomy cells." Although they used Mallory's stain for some slides, their photomicrographs are of sections stained with hematoxylin and eosin, and this staining method is such as to make it impossible to recognize the "thyroidectomy cells," because with eosin it is impossible to distinguish between the smooth hyalin intracellular material and the granular cytoplasm, and hematoxylin is inadequate for differentiating basophils.

Human autopsy material has been studied by a number of Germans. Wegelin¹⁹ found that the pituitary of a cretin man aged 56 showed fatty degeneration of the chief cells, eosinophils and to a lesser degree of the basophils. Eosinophils and basophils were reduced in numbers. He describes the presence of many cells which he calls transition cells according to the terminology of Kraus,

larger than chief cells, with no granules and staining red with eosin. Abrikossof¹ found the pituitary of a woman aged 52 who had been myxedematous since 25 years of age to show an increased size of chromophil cells. MacCallum and Fabyan⁹ found in the case of a 13-year-old cretin that the chromophobe cells were enlarged, the basophils very abundant and striking, and that some eosinophils were present but shrunken. Schilder¹³ described in human hypothyroidism the appearance of a new cell which may develop from a chromophil or chromophobe. He regarded this cell as similar to Erdheim and Stumme's "Schwangerschaftszellen." He believed that there was probably increased activity and made the suggestion, keen considering the state of knowledge concerning the pituitary at that time, that the clinical manifestations of hypothyroidism are not to be attributed solely to the lack of thyroid but are attributable also to changes in the pituitary. Schultze¹⁴ described in a case of aplasia of the thyroid in a woman aged 26 a reduction in number of acidophils and basophils with the presence of an adenoma of chief cells.

Summary. When thyroidectomy is performed in young rats there results stunting of body growth, an increased weight of the pituitary due both to increased solids and increased fluid content; a marked reduction or nearly complete disappearance of acidophils; an increase in the number of basic staining cells; and the appearance of great numbers of large cells filled with hyalin substance. These "thyroidectomy cells" appear, according to the special staining technique used, to be transformed cells containing blue granules.

The "thyroidectomy cells" appear to be secreting and storing a secretory product which is hyalin in appearance.

It is suggested that the stunting of body growth in the cretin rat may be due to loss of acidophils of the pituitary which in turn depends upon loss of the thyroid secretion. Acidophils seem to disappear by degranulation rather than by frank degeneration. An abundance of thyrotropic hormone was found to be present in cretin pituitaries depleted of acidophils, a finding which rules out the acidophil cell as the producer of thyrotropic hormone. Since there is no atrophy of the adrenals in cretin rats, it is reasonable to consider that the acidophils cannot be the producers of the adrenotropic hormone. When thyroidectomy is incomplete, the above changes are slight or absent.

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COMPLETE INSULIN RESISTANCE IN DIABETES.

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THE announcement of the successful treatment of diabetes mellitus with insulin was hardly confirmed and put on a sound basis before there began to appear in medical literature reports of resistance to its action. Many of the earlier cases of so-called insulin resistance, however, could in the words of Labbé¹ be attributed to poor management or errors in interpretation.

On the basis of the experimental work of Hedon and McLeod on depancreatized dogs, Root² estimated that a completely depancreatized man would require 200 to 300 units of insulin daily. Undisputed cases of complete insulin resistance in man would then be those which have a daily requirement above this figure; *i. e.*, representing a complete replacement of the amount of insulin which

the body itself is capable of forming. A rather careful search through the literature reveals very few such cases excepting those which first come under observation when in coma and are given an enormous dosage before they either recover or die.

In 1927 Lawrence³ reported the case of a 19-year-old boy, who had had diabetes for 2 years, whose insulin requirement had gradually risen, until, on a diet of carbohydrate, 115; protein, 80; fat, 150; he was excreting 55 gm. glucose in the urine despite 220 units of insulin daily. One day 400 units were given without inhibiting the rise of blood sugar after food. Insulin was then stopped for 5 days. At the end of this period the patient was in profound ketosis. He was rescued with insulin. For a time after this it was found that 80 units a day controlled the diabetes, although the requirement later rose to 160 units.

Glassberg, Somogyi and Taussig⁴ described a case of a woman with diabetes which, beginning mildly, rapidly became more severe. At one time there was a skin sensitivity to insulin. The insulin requirement gradually increased over a 9-month period. In the course of the next 3 months she received an average daily dose of 317 units of insulin. In spite of this, acidosis occasionally intervened, requiring amazingly large dosage—1100 units in 1 day. Contrary to the usual experience 1 dose seemed more effective than divided dosage. This woman spontaneously improved and later behaved like an ordinary severe diabetic.

More cases of insulin resistance are reported in connection with hemachromatosis than with any other disease. Root² reported the case of a physician who had known hemachromatosis for 4 years. In the course of a few months he became increasingly resistant to insulin. In the last $1\frac{1}{2}$ months of life the dosage was advanced progressively from 525 to 1600 units daily, without material benefit.

Allan and Constam⁵ observed for 2 months a man with hemachromatosis who used 500 units of insulin daily. One of Wegner's patients⁶ required 300 units of insulin daily to eliminate glycosuria. The case observed by Wood and Fitzhugh⁷ continued to have glycosuria on 175 units daily and larger doses had little effect. Engel's patient⁸ had had diabetes for 9 years, doing fairly well without insulin until a short time before admission in a precomatose state. The acidosis cleared with fairly small doses of insulin but the blood sugar remained high. Although the insulin dosage was advanced to around 200 units daily, the glycosuria persisted; shortly before death 1365 units were given in 1 day but sugar was found in the urine.

Karr, Skull and Petty⁹ treated a diabetic who had a marked skin sensitivity to insulin. Her insulin requirement gradually increased, until, over a 4-month period she was receiving 470 to 620 units daily. Various kinds of insulin were given with no success. All tests indicated she was sensitive to insulin *per se*. Rabbits were

sensitized to the patient's serum. The patient was then given intramuscularly 5 cc. of this sensitized rabbit serum. In 1 week the insulin dosage was dropped to 150 units daily and after a month it was found possible to discontinue it.

That insulin may be comparatively ineffectual during acidosis is a very well-known phenomenon. A few cases which received an extraordinarily large dosage may be mentioned: Byworth¹⁰ gave a diabetic with tuberculosis 1715 units. The patient was later discharged in good condition on 110 units daily. Labbé and Boulin¹¹ followed a case which received 3850 units in 13 days. Pollack and Long¹² report a case admitted in acidosis, successfully treated and carried for 6 days on 90 to 130 units daily. On the 7th day he relapsed into acidosis. He received 470 units this day and 540 units on the next. Because of a large thyroid gland iodine was given. The patient went into shock and died the following day. Necropsy showed thrombosis of all branches of the celiac artery.

Rudy¹³ had a patient with mild diabetes who developed urticaria followed by temporary resistance to insulin. She was given 515 units in 24 hours. After this it was possible to decrease the dosage until none was required by the 11th day.

Falta and Boller¹⁴ and MacBryde¹⁵ working in Falta's Clinic, report a series of cases in which relative resistance to insulin is brought out. Mauriac,¹⁶ Serio,¹⁷ Häusler and Höglér,¹⁸ Umber and Rosenberg¹⁹ and others believe in this type of partially resistant diabetes. Such resistance can be gauged by the lack of blood-sugar response to small or to large doses of insulin.

Case Report. M. P. (184535), a 44-year-old, white, divorced telephone operator, entered the San Francisco Hospital for the third time on June 11, 1934.

For several years she had had an intermittent dry cough. For a year this cough had been productive of sputum which later became blood streaked. In 6 months she had had two hemoptyses of 2 ounces each. She had also developed night sweats, afternoon fever, weakness and easy fatigue. Several weeks before admission she was examined by a doctor who told her she had cavities in the lungs. She had lost 50 pounds in a year.

Family History. Was negative for tuberculosis. Mother had pernicious anemia.

Past History. Included pneumonia in 1904 and 1909, influenza in 1918. Diabetes was discovered in 1930. She was in this hospital in 1930 with the diagnosis of pelvic inflammatory disease. A supravaginal hysterectomy and bilateral oophorectomy were done. She had on this admission some dysuria and nocturia.

Physical Examination. An emaciated pale woman lying in bed and coughing frequently. In the mouth were a few loose teeth. No lymphadenopathy. The chest showed bilateral wasting. There was dullness over both upper lobes, with flatness and tubular breathing over the right upper lobe anteriorly. Moist râles were heard through the right lung, a few râles at the left sternal border. The heart was not enlarged; sounds were loud and regular. Blood pressure 125/80. There was a hernia of a midline lower abdominal scar.

Laboratory. Hemoglobin, 73%; red blood cells, 3,900,000; white blood cells, 10,200 with 52% neutrophils. Urine, acid; specific gravity, 1.018; glucose 3+; acetone plus; few pus cells in sediment. Sputum repeatedly positive for acid-fast bacilli. Wassermann reaction negative. Sedimentation 28 mm. in 1 hour (Cutter). Fasting blood sugar 282 mg/100 cc.

Roentgen Ray Report. "Extensive pulmonary tuberculosis with multiple cavitation."

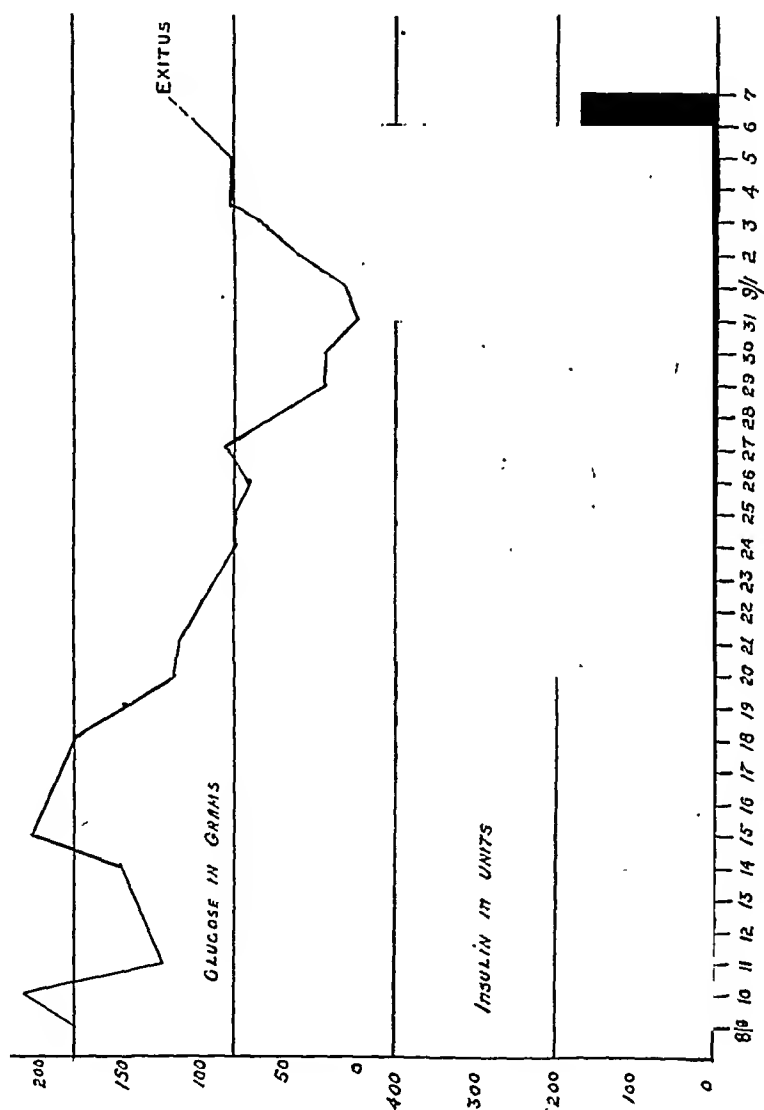


CHART I.—Daily insulin dosage compared with glucose excretion.

Course. She was never afebrile for more than a few hours, there was a daily rise to 99 or 100° F. with occasional elevations to 102°. The diabetes was at first controlled on a diet of carbohydrate, 175; protein; 75; fat, 75 with insulin 45-0-35-12 (92 units daily). A month after admission, while on the same intake, she began again to excrete large amounts of sugar into the urine. The fasting blood sugar which had been 143 mg/100 cc. rose to 256 mg. She was kept on the same diet and her insulin dosage

was increased. On August 15 she received 165 units of insulin and excreted 205 gm. glucose. By August 27 she was receiving 320 units daily while she excreted over 87 gm. glucose (Chart I). The diet was changed to 160-60-60 while the insulin dosage continued to be pushed up. For a time she seemed to be under better control, excreting only 7 gm. on August 31 while receiving 400 units of insulin. However, although she was being given 415 units daily, she again began to excrete more and more glucose, *e. g.*, 122 gm. on September 5. On September 6 she was reduced to 70 units. This day she excreted 125 gm. of glucose, had an urinary output (4345 cc.) considerably higher than it had been and a 4+ test for acetone in the urine. At 5.00 A.M. the next morning early signs of coma were observed. In spite of prompt efforts to relieve her (including another 100 units of insulin) she became unconscious at 8.00 A.M. and died at 11.45 A.M.

AUTOPSY (Dr. Alvin Cox). There are many adhesions over both apices, over the left diaphragm, through the posterior portion of the right pleural cavity and in the interlobar fissures. Extensive cavitation is found in both upper lobes. Caseous tuberculosis is found through both lungs, the left lower lobe being least affected. The peribronchial lymph nodes are moderately enlarged; some show a few gray nodules. The pancreas is grossly normal in size and appearance. The uterus has been amputated just above the cervix. The tubes and ovaries are surgically absent. The other organs are normal.

Microscopic Examination. Smears from the left pleural cavity show clusters of slender acid-fast bacilli. Sections from the lungs show variously areas of caseous pneumonia, fat-containing phagocytes, edema, conglomerate tubercles and fibrosis. There is slight fatty infiltration of the pancreas. The Islands of Langerhans and the acini appear normal. Special fixation and staining reveal no glycogen. The liver shows slight fatty infiltration but no glycogen. The kidneys show slight cloudy swelling and fatty infiltration. No glycogen is found. A peribronchial lymph node demonstrated several tubercles with giant-cell formation and caseation. The colonic mucosa contains eosinophils.

Comment. This woman was, before June, 1934, a diabetic of moderate severity who was also suffering from bilateral pulmonary tuberculosis, both of which were steadily advancing. On July 20 she was sugar-free on a diet of carbohydrate, 175; protein, 75; fat, 75; and 87 units of insulin. In the course of a very few days she showed very large amounts of sugar in the urine despite huge and increasing doses of insulin.

The attempt was made to keep her on a diet sufficient for the tuberculosis and to cover the deficiency of carbohydrate metabolism with enough insulin. For a time it seemed as though this might be successful. Later when it obviously was not, an attempt was made to reduce the insulin dosage abruptly.³ This was, as is seen, followed by a quick exitus.

It is reasonable to suppose that had the insulin dosage been further increased, the result would have eventually been the same, as was the case with Root's patient.²

From a study of the chart it will be seen that this patient's ability to utilize sugar was enhanced by the use of extraordinarily large amounts of insulin, but that it was apparently impossible to keep her from excreting sugar into the urine until something happened

within her own organism to reduce her resistance. During this spontaneous partial remission very little glucose appeared in the urine. Then, on doses of insulin larger than before, her resistance again increased until there was as much sugar in the urine on 415 units daily as there had been 3 weeks before on 200.

However, the proof that the insulin, far in excess of what could be utilized, was serving a purpose is shown in the fact that within 18 hours after a smaller dosage was attempted the patient was in coma and within 28 hours she was dead—although the amount of insulin was still far in excess of that ordinarily sufficient.

Certain characteristics of the few cases of complete insulin resistance reported may be observed: (1) The resistance, as measured by the amount of insulin necessary to prevent glycosuria appears relatively quickly, usually over the period of a few months, and increases progressively. (2) The tolerance to insulin is usually proportional to the resistance—evidence of hypoglycemia is rare (in this case there were periods of asserted shock, unfortunately never checked chemically). (3) The obvious precipitating factors are various—severe liver and pancreatic disease, allergy, endocrine disturbance, and in this case, infection. It is interesting, that despite the relatively common occurrence of severe tuberculosis coincident with diabetes, no case of complete resistance in connection with infection was found in the literature. (4) There seems to be a tendency in some cases, at least, for the resistance to disappear spontaneously. It may almost be ventured that the phenomenon of complete resistance to insulin is an independent one, coincident with, rather than caused by the apparent etiologic factors, and disappearing after a period of time, if death has not been caused by the concurrent disease and provided enough insulin has been given during the resistance period. The remissions in the case of Glassberg and his colleagues have no apparent relationship to the treatment. Lawrence's case improved paradoxically after the cessation of insulin with the appearance of ketosis. A tendency to excrete less and later more glucose in the urine regardless of the insulin dosage may be seen in Chart I. Such reasoning may not hold good in hemachromatosis where anatomical changes are obvious and resistance seems concomitant with the end stages of the disease.

Although the etiology of resistance to insulin is not known, most observers agree in placing the responsible factors outside of the pancreas. Häusler and Högler¹⁸ and Häusler and Loewi,²⁰ investigating the occurrence of an insulin-antagonistic substance in the blood, found that less glucose was taken up by human erythrocytes *in vitro* from the plasma of human insulin-resistant diabetics and from the plasma of dogs with the pancreas completely removed. They concluded that the cause of the resistance lies in the inaccessibility of the body cells to the action of insulin. This substance was

named "Glykämin."²¹ Allan and Constam⁵ failed to confirm these experiments.

Himsworth²² has brought forth evidence to indicate that the insulin excreted by the pancreas is inactive and requires an unknown activator to transform it into utilizable substance. The absence of this companion substance in the blood could conceivably result in the phenomenon of insulin resistance.

That the liver plays a large rôle in the production of insulin resistance is indicated in the preponderance of cases with liver disease and by the importance of the liver in carbohydrate metabolism. The existence of an anti-insulin in the liver has been postulated²¹ but has not yet been proven.

Summary. A case of diabetes mellitus, complicated by pulmonary tuberculosis, in which extraordinarily large amounts of insulin were insufficient to check the glycosuria, is presented. Death occurred after an attempt was made to reduce the insulin dosage. The case is regarded as an example of complete insulin resistance and is discussed in relation to other cases of insulin resistance previously reported.

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A STUDY OF BLOOD SUGAR OF EPILEPTICS.

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IN 1924, Harris¹ called attention to the occurrence of hyperinsulinism and the resulting hypoglycemia. Subsequent papers by the same author^{2,3} show that hypoglycemia is associated with convulsions similar to epileptiform seizures which in some cases have been diagnosed as epilepsy. As the data available on the blood sugar of epileptics are limited, it was felt that a study of a fairly large number of epileptics would be of value.

At Pacific Colony, a state institution for feeble-minded and epileptics, there are over 150 patients whose condition has been diagnosed as idiopathic epilepsy. From this group, 92 patients were chosen for fasting blood sugar determinations; 16 non-epileptic patients in the same institution, whose diet and living conditions were similar, served as a control group.

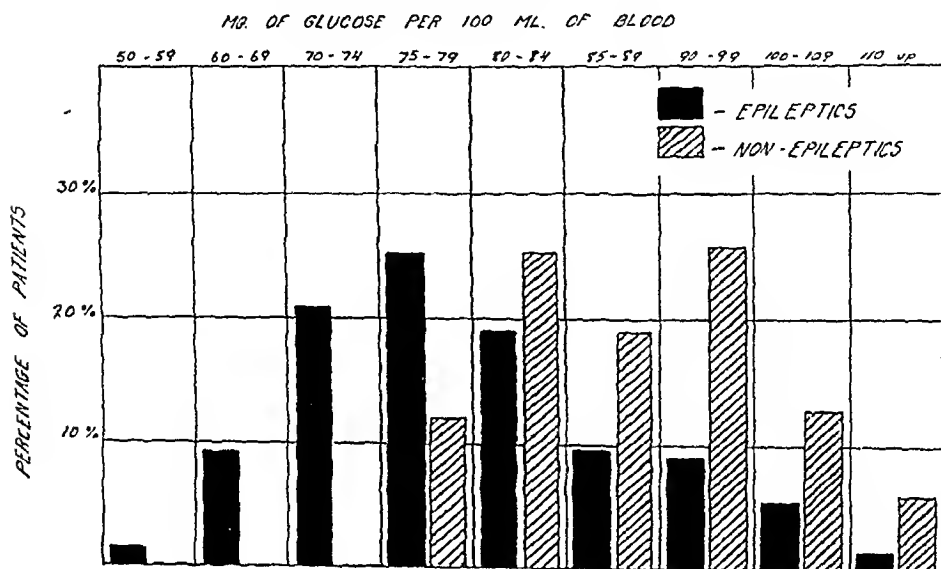
The blood samples were taken between 10.30 and 11.00 A.M., approximately 4 hours after breakfast. (This time was suggested by Dr. Harris in a private communication.) Five milliliters of blood were withdrawn from a vein in the arm and analysis was started immediately. The standard Folin and Wu method for the determination of glucose in blood was used throughout the study.

A summary of these tests is given in Chart I. It is apparent that as a group the epileptic patients showed an abnormally low amount of sugar in their blood. If 80 mg. of glucose per 100 ml. of blood is regarded as the lowest level for a normal fasting blood sugar value, 56.4% of the epileptic patients as compared with 12.5% of the control group show subnormal fasting blood sugar values.

In order to test the constancy of the fasting blood sugar level of epileptic patients, repeated determinations were made on 9 of the patients (Chart II). While a wide variation is seen, it is also noted that none of the patients showed a fasting blood sugar value that

was consistently normal; 11% showed values that were always subnormal; and 67% of the patients showed values that were normal only 50%, or less, of the times tested. While these results show that a single fasting blood sugar determination of an individual is of questionable value, the data obtained from such a large group seem to demonstrate the tendency of the group as a whole toward subnormal fasting blood sugar values, as do repeated fasting blood sugar determinations of an individual.

CHART I.—DISTRIBUTION OF FASTING BLOOD SUGARS FOR EPILEPTICS AND NON-EPILEPTICS.



Of the 92 epileptic patients whose fasting blood sugars were determined, 85 were receiving luminal (phenobarbital), as were the 9 patients whose fasting blood sugars were rechecked over a period of time. The dosage varied from 0.5 to 4.5 grains daily. It has been suggested that perhaps the drug itself functions in raising the blood sugar level.³ To investigate this possibility, a non-institutionalized control took two 1.5 grains of luminal during a period of 12 hours. This resulted in an increase of 7% in the fasting blood sugar level, which was normally very constant and on three different tests covering several months showed a variation of less than 1%. When the symptoms caused by the drug began to wear off, the blood sugar value dropped slowly. While this is not conclusive evidence that luminal does raise the blood sugar level, it at least supports an existing theory. If luminal actually does raise the blood sugar level, there would be more than 56.4% of the epileptic patients showing subnormal sugar values if luminal therapy were not used.

Glucose tolerance tests were made on 7 epileptic patients who were chosen because of their normal mentality and willingness to

coöperate in the experiment. Although they were ordinarily on luminal therapy, the drug was not given the night preceding nor on the morning of the test, nor was smoking allowed. The fasting blood sugar was taken at about 8.00 A.M. Immediately thereafter the patient drank a 50% solution containing 100 grams of glucose. Sugar determinations were made at approximately half-hour intervals for the first 2 hours, and at hourly intervals for the following 4 hours.

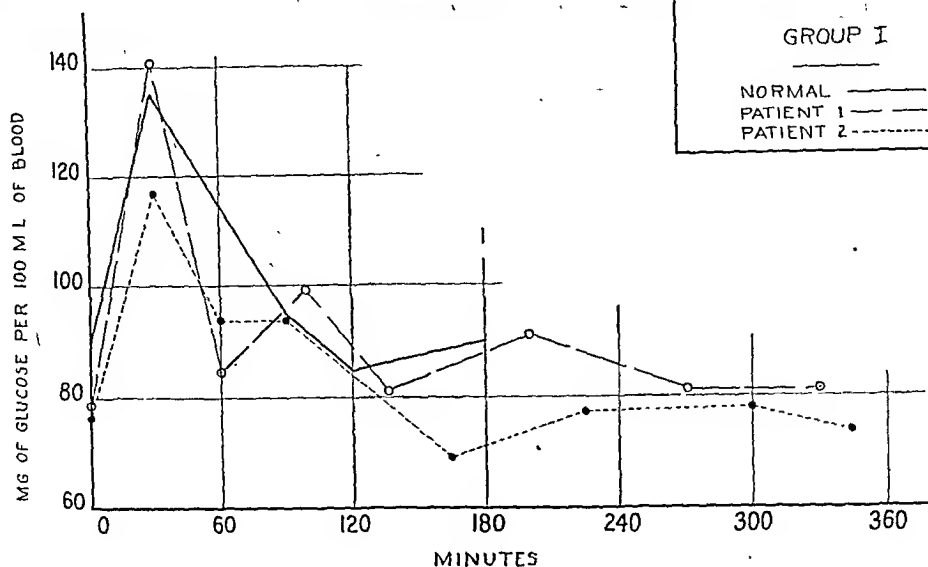
CHART II. VARIATION IN FASTING BLOOD SUGAR VALUES.

Patient number.	Date (all in 1934).	Blood sugar in mg. per 100 ml. of blood.	Per cent of difference between lowest and highest value.	Per cent of the times tested when normal sugar values were obtained.
1	4/9	111		
	5/7	69		
	5/10	90		
	6/22	80	39	75
2	4/9	98		
	5/7	95		
	7/5	76	29	67
3	4/9	90		
	5/7	76		
	5/10	76		
	7/6	100 ¹	31	50
4	4/9	104		
	5/7	73		
	5/10	79		
	7/27	80	42	50
5	5/10	73		
	5/13	66		
	7/20	75	13	0
6	5/31	74		
	10/12	90		
	10/26	76	22	33
7	4/9	94		
	5/7	72		
	6/29	82	30	50
8	4/9	69		
	5/7	74		
	7/13	76	10	0
9	4/9	86		
	5/7	62		
	5/10	88	45	67

The experimental curves obtained from the glucose tolerance tests fall into three groups, as shown by Graphs I, II and III. On the three graphs the experimental curves are contrasted with the normal curve taken from Bodansky.⁴

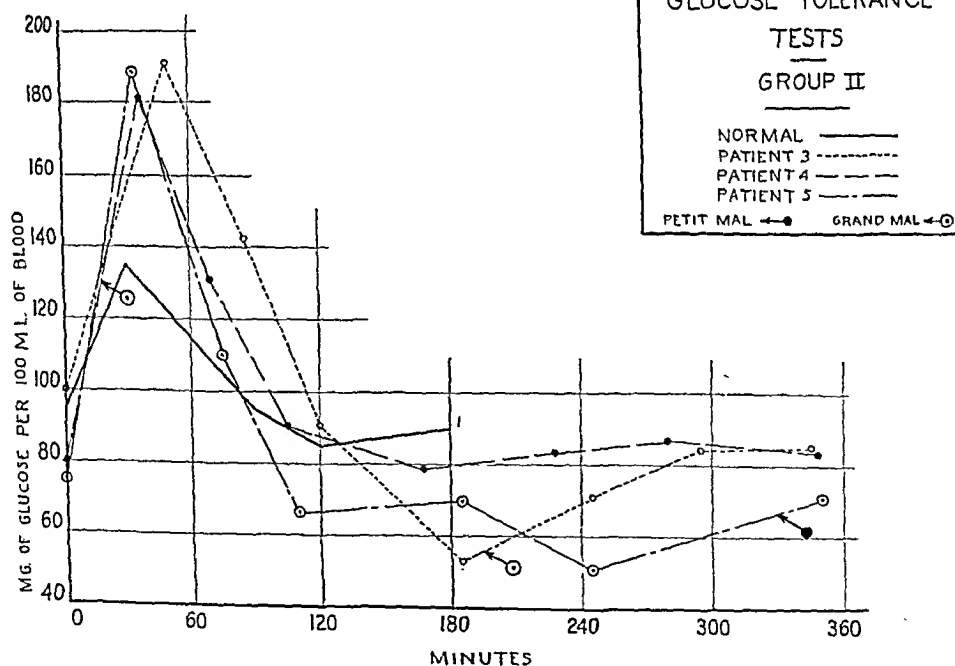
Group I. Curves that do not deviate greatly from the normal curve. Patients in this group average but one grand mal seizure every 2 months.

GLUCOSE TOLERANCE
TESTS
GROUP I



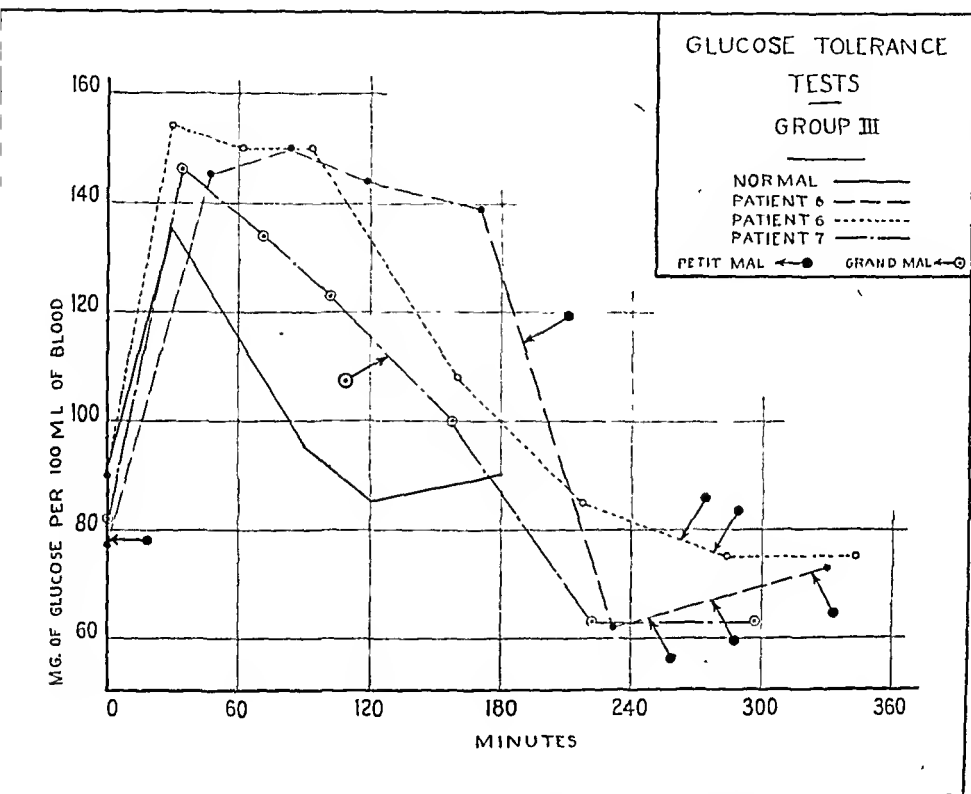
GROUP I. Type of curve nearest normal. No seizures occurred during test. In the first 11 months of 1934, Patients 1 and 2 each had 5 seizures.

GLUCOSE TOLERANCE
TESTS
GROUP II



GROUP II. Abnormal type of curve. Patient 3 had 2 grand mal seizures and Patient 5 had 1 petit mal seizure during the test. In the first 11 months of 1934, Patient 3 had 44, Patient 4 had 13, and Patient 5 had 35 grand mal seizures. Patient 5 also had many petit mal seizures.

Group II. Exaggeration of peaks and valleys. Curves whose maximum peaks are from 40 mg. % to 50 mg. % higher than the normal peak and whose minimum values are from 5 mg. % to 34 mg. % lower than the normal curve. The general contour of the experimental curves is similar to the normal one, but the peaks and valleys are greatly exaggerated. The patient (Case 4) whose minimum value is only 5 mg. % below the normal amount, averages but one grand mal seizure per month. The patients (Cases 3 and 5) whose minimum values are 31 mg. % and 34 mg. % below the normal value average from 3 to 4 grand mal seizures per month.



Group III. Most abnormal type of curve. Patient 6 had 3 petit mal seizures during 1 test, and 5 petit mal seizures during the second test several weeks later. Patient 7 had 1 grand mal seizure during the test. Patient 6 had 9 grand mal seizures from the date of his admission, May 19, to December 1, 1934, and in addition had averaged about 5 petit mal seizures per day. Patient 7 had 68 grand mal seizures in the first 11 months of 1934.

Group III. Delayed return to minimum values which are sub-normal. Curves which rise similarly to the normal curve for the first half hour but which do not return to the minimum value for from $3\frac{3}{4}$ to $4\frac{3}{4}$ hours instead of the 2 hours exhibited by the normal curve, and the minimum values are much lower than shown in the normal curve. One patient in this group (Case 6) averages about

2 grand mal seizures per month and 5 petit mal seizures per day. The other patient in this group (Case 7) averages 6 grand mal seizures per month. It should be noted that two tests were run on Patient 6 and very similar curves were obtained in each case.

Summary. Abnormal carbohydrate metabolism appears to be associated with at least one type of epilepsy, as shown by the two series of tests here presented.

1. A study of the fasting blood sugar level of 92 epileptic patients showed that although 85 of them were on luminal therapy, which may cause a rise in the fasting blood sugar level, 56.4% of the group showed subnormal fasting blood sugar levels as compared with only 12.5% of the non-epileptic control group.

2. The glucose tolerance tests pointed strongly to the fact that there is a correlation between abnormal glucose tolerance and the frequency of the seizures experienced by the patients, both during the test and during the patients' institutional life. However, the seizures that occurred during the tolerance tests were as likely to occur at medium as at low blood sugar values. Three types of response to the sugar tolerance test by epileptics are discussed.

We wish to express our appreciation for the assistance given the writers by Mr. H. L. Roberts, Mrs. Pearl McRae and Mrs. Dorothy K. Tyson of Pacific Colony, and by Dr. L. W. Case of the Pomona Valley Community Hospital. Without their generous coöperation this study would have been impossible.

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THE RELATION OF EXPERIMENTAL SKIN INFECTION TO CARBOHYDRATE METABOLISM.

THE EFFECT OF HYPERTONIC GLUCOSE AND SODIUM CHLORID SOLUTIONS INJECTED INTRAPERITONEALLY.*

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THE occurrence of infections of the skin, often of unusual severity, is frequently noted as a complication of diabetes (van Noorden

* This research was aided by a grant from the Faculty Research Committee of the University of Pennsylvania.

and Isaac,¹ Greenwood²). Aside from the vascular disease which is sometimes present, an adequate explanation of this phenomenon is lacking and there has been surprisingly little study of it experimentally. It has also been proposed, but not definitely established, that skin infections may occur as a result of excessive ingestion of carbohydrates by non-diabetic individuals.

The presence of increased amounts of glucose in the skin cannot apparently be regarded as the sole explanation of the lessened resistance of diabetics to infection. Greenwood and Rockwood,³ on the basis of a study of a series of diabetic patients having an average blood sugar of 198 mg. over a period of 5 years, found that only 5% of such patients developed skin infections, although fungi were recovered from the feet of 70% of their cases and staphylococci from the feet of 100%. They conclude that some other factor than the hyperglycemia must be operative. Fabry⁴ has expressed a similar opinion.

Richardson⁵ has recently demonstrated that the blood of diabetics is deficient in antibacterial power, due to an impairment of the amboceptor rather than from any lack of activity of the complement. He found that this was true of both the natural amboceptor as shown by bactericidal tests and the acquired amboceptor as shown by the increased ability of the blood to form agglutinins. Kleinschmidt⁶ found that diets excessive in carbohydrates or fat produced no marked difference in antibody formation in non-diabetic dogs. Handmann⁷ has shown that blood to which 0.5 to 1.5% of glucose was added maintained its bactericidal power for staphylococci *in vitro*.

We have encountered only a single study of the effect of glucose on experimentally induced infection. Franceschelli⁸ has observed a heightening of the virulence of streptococci when phlorizin diabetes was induced in rabbits. No effect on the virulence of staphylococci was noted, however, nor did the injection of large amounts of glucose into phlorizinized rabbits result in any change in the virulence of bacteria.

Cornbleet⁹ has observed a retardation of the self-sterilizing powers of the skin following administration of 50 to 100 gm. of glucose daily to patients. Since the degree of retardation appeared to be related to the slowness with which the blood sugar returned to the fasting level, Cornbleet believes that the infections of the skin which he has observed in patients with a lowered carbohydrate tolerance may be dependent on this factor. Usher¹⁰ has shown that increases of sugar in the sweat of diabetics may lead to more favorable conditions for the growth of fungi and bacteria.

Numerous attempts to demonstrate a connection between decreased carbohydrate tolerance and infections of the skin by means of fasting blood-sugar determinations and glucose-tolerance tests have been made. The results of such studies are contradictory,

as will be seen from the summaries of the literature by Fischer¹⁸ and by Rudy.²¹ Pick,¹¹ Müller,¹² Simon,¹³ Devoto,¹⁴ Benet, and Nepveux¹⁵ have reported increased blood-sugar levels in patients with furunculosis; Schamberg and Brown,¹⁶ Rost,¹⁷ Fischer,¹⁸ and Narducci¹⁹ note no significant increase; while Tauber²⁰ reports hypoglycemia to be a frequent finding and has noted a favorable response to intravenous injections of glucose in furunculosis.

To summarize this brief review of pertinent studies, most of which are as yet unconfirmed, it is indicated: (1) that while diabetics show a somewhat increased incidence of skin infections, some severe diabetics may have an entirely normal resistance to such infections and that the presence of increased glucose in the skin is not, apparently, the sole reason for decreased resistance to infection, (2) that the blood of diabetics is deficient in antibacterial power, but (3) that a heightened intake of carbohydrate in normal dogs leads to no marked decrease in antibody formation and that the simple addition of considerable quantities of glucose to blood does not lessen its bactericidal power for staphylococci; (4) that phlorizin diabetes heightens the virulence of streptococci but not of staphylococci in rabbits; (5) that administration of glucose in humans apparently decreases the self-sterilizing power of the skin; and (6) that it is doubtful whether or not decreased carbohydrate tolerance is more frequently encountered in patients with skin infections than in normal individuals.

In view of the contradictory nature of much of the clinical evidence concerning the influence of carbohydrate on skin infections and the marked paucity of experimental evidence, particularly in animals, we have undertaken a study of the effect of parenteral administration of comparatively large amounts of glucose on the course of experimentally induced skin infections in rabbits.

Method. Considerable preliminary work on the method of consistently producing skin infections was necessary. We obtain only an occasional infection following intradermal injection of a suspension of *Trichophyton gypseum* in rabbits. Using various strains of staphylococcus and streptococcus injected intradermally in broth suspension, infection was obtained in a large proportion of rabbits with staphylococcus, but in less than half the animals with streptococcus. A greater or less degree of reaction was present in all animals injected with a bacterial suspension, but based on the criterion of recovery of the organism, successful inoculation was considerably less using streptococci than with staphylococci. In successful infections the degree of reaction to staphylococcus was greater than that to streptococcus. There was no evidence of symbiotic effect when the two organisms were injected mixed in the same broth suspension. The degree of reaction, while somewhat dependent on the amount of bacterial suspension injected, was not nearly proportional to it. Intradermal injection of sterile broth medium produced no reaction.

By successive inoculation and recovery of the organism from rabbits we obtained a strain of *S. aureus hemolyticus* originally isolated from a case of pyoderma, which always produced definite infection in the skin when injected intradermally. In normal rabbits, following intradermal injection

of 0.5 cc. of a broth suspension of the organism, the resulting infection varied from an inflammatory nodule 3 cm. in diameter, with a small central ulcer, to an ulcer 3 cm. in diameter surrounded by an indurated inflammatory border 0.5 to 1 cm. wide. Infections of the latter extent were uncommon, only 3 such being encountered in control rabbits. Twenty-four-hour broth cultures were used throughout, no bacterial count being done on the suspensions. In each set of experiments the same suspension was used for intradermal injection in both the control and the glucose-injected animals. While none of the data here presented are based on observation of rabbits previously infected, we noted no evidence of acquired resistance to the organism following repeated infection of the same animal.



FIG. 1.—Infection of skin of normal rabbit 72 hours after intradermal injection of suspension of hemolytic *Staphylococcus aureus*.

Varying amounts of 50% glucose solution were injected intraperitoneally at varying intervals in animals infected intradermally. The initial injection of glucose was made within a few minutes after the injection of the suspension. The infection was produced high on the abdomen and the intraperitoneal injections given low down, well away from the site of infection.

Exact interpretation of the degree of inflammatory response following intradermal injection of a bacterial suspension is difficult because of the variation of the infection in control rabbits and because of the variety of criteria which may be considered. It was felt, after considerable observation, that the extent of the resulting ulceration represented the most reliable

and significant change. The extent of the inflammatory response did not always forecast a severe destructive change. The duration of the infection until definite involution was noted was a helpful criterion, but in our later experiments the rabbits frequently did not survive until healing had begun.



FIG. 2.—Extensive necrotic infection of the skin of rabbits receiving 24-hour total of 15 gm. glucose per kilo injected at intervals of 4 hours. Skin infected 36 hours previous to time of picture.

Results. In Table 1 it is seen that intraperitoneal administration of as much as 7.5 gm. of glucose per kilo in 2 doses in 24 hours did not affect the course of the experimentally produced staphylococcal skin infection. While such injections constituted a large total dose of glucose, it was found that the blood sugar was raised during only about 10 hours of the 24. It was therefore decided to produce a more continuous and marked hyperglycemia by frequent injections of glucose although the possibility of producing changes in water balance was apparent. It was found that following an injection of 2.5 gm. glucose per kilo the blood sugar returned to normal in about 5 hours. Repeated injections were therefore given every 4 hours. The peak of the blood sugar rise was reached in about 30 minutes after injection and in 4 hours the value was usually above 200 mg.%. While we were not able to follow fre-

quently the blood-sugar values over a period of 36 to 48 hours, our data indicate heightening of the peak of the blood sugar following successive injections, a slower fall toward normal, and an increasing failure to approximate the normal level.

TABLE 1.—THE EFFECT OF INJECTIONS OF GLUCOSE INTRAPERITONEALLY AT INTERVALS OF 24 AND 12 HOURS ON THE EXPERIMENTAL SKIN INFECTION.

Exp.	No. of rabbits.	Glucose per kilo, total in 24 hours.	Injection interval, in hours.	Duration of exp. in days.	Course of skin infection.
I	2 injected 1 control	2.5 gm.	24	4	All infection in normal range; infection in one glucose animal more, and in other less marked than in control.
II	2 injected 1 control	4.0 gm.	24	5	Infection of one glucose animal slightly more marked, the other less marked than control.
III	3 injected 3 controls	4.0 gm.	24	6	Two glucose animals showed less reaction than all controls; one showed more reaction. All infections within usual limits of control animals.
IV	3 injected 2 controls	7.5 gm.	12	6	All infections within usual limits; one control showed slightly more reaction than glucose animals, the other slightly less.
V	3 injected 2 controls	7.5 gm.	12	6	All within usual limits.
VI	2 injected 2 controls	7.5 gm.	12	6	All within usual limits.

TABLE 2.—THE EFFECT OF INJECTIONS OF 50% GLUCOSE INTRAPERITONEALLY AT 4-HOUR INTERVALS ON THE EXPERIMENTAL SKIN INFECTION.

Exp.	No. of rabbits.	Glucose per kilo, total in 24 hrs.	Injection interval, in hrs.	Course of skin infection.	Result.	No. of injections.
VII	4 injected	15 gm.	4	No. 1: ulcer 10.5 x 9 cm. 36 hours after first glucose injection	Recov.	11
				No. 2: ulcer 11 x 12 cm. 30 hours after first injection; marked diarrhea	Died	6
				No. 3: ulcer 14 x 12 cm. 30 hours; marked diarrhea	Died	7
				No. 3: ulcer 13 x 10.5 cm.	Recov.	11
				All infections within usual limits		
VIII	4 controls	No. 1: ulcer 8 x 8 cm.	Died	9
	4 injected	15 gm.	4	No. 2: ulcer 4 x 3 cm.	Died	11
				No. 3: ulcer 8 x 10 cm.	Recov.	10
				No. 4: ulcer 6 x 8 cm.	Died	10
	3 controls	All within usual limits; no ulcer over 1.5 cm. in diameter in 48 hours		

Eight rabbits were given 2.5 gm. glucose per kilo every 4 hours for periods varying from 36 to 48 hours. The skin infection of all 8

showed not only a marked variation in extent as compared to control animals but also a difference in character, consisting of a lessened degree of inflammatory reaction at the periphery of the infected area and a gangrenous necrotic appearance of the ulcer with less production of frank pus. The entire course of the infection was one of astoundingly rapid advance, with demonstrably less evidence of local tissue resistance to the infection.



FIG. 3.—Skin infection 36 hours after intradermal injection of staphylococcic suspension in rabbit receiving hypertonic NaCl solution intraperitoneally at intervals of 4 hours.

Of these 8 rabbits 5 died in from 3 to 7 days after the initial injection of glucose. Postmortem examination revealed little or no peritoneal fluid; a small amount of free pus was present in one animal in which perforation of the large bowel was present. The liver, spleen, pancreas, and intestines of the animals were grossly normal. Routine hematoxylin and eosin sections of the liver revealed no marked changes.

To determine whether or not the hypertonicity of the injected glucose was responsible for the marked increase in the extent of the infection in animals injected frequently, control experiments were performed in which a solution of sodium chlorid of approximately

the same tonicity as 50% glucose solution was injected. It will be seen from Table 2 that the extent of the skin infections following such injections was markedly greater than in normal rabbits and that it closely approximated the infection noted after frequent injections of glucose. In 4 animals, two of which received 4% NaCl and two 2% NaCl solution, the course of the skin infection was similar to that of the control animals.

TABLE 3.—THE EFFECT OF INJECTION OF NaCl SOLUTION OF VARYING STRENGTHS INTRAPERITONEALLY ON THE EXPERIMENTAL SKIN INFECTION.

No. of rabbits.	Strength NaCl, %.	NaCl in cc.	Injection interval in hrs.	Course of skin infection.	Result.	No. of injections.
4	9	10	4	No. 1: ulcer 5 x 7 cm. No. 2: ulcer 9 x 7 cm.; markedly toxic No. 3: ulcer 6 x 7 cm. No. 4: ulcer 3 x 4 cm.	Recov. Died	8 6
2	4	10	4	No. 1: ulcer 2 x 2 cm. No. 2: ulcer 1.5 x 2 cm.	12 12
2	2	10	4	No. 1: ulcer 1 cm. in diameter No. 2: ulcer 1.5 cm. in diameter		
2	—Control—	—	—	No. 1: ulcer 2 cm. in diameter No. 2: ulcer 1.5 cm. in diameter		
3	9	10	4	No. 1: ulcer 5 x 3 cm. No. 2: ulcer 4 x 4 cm. No. 3: ulcer 8 x 10 cm.	Died Died Recov.	6 7 10
2	—Control—	—	—	Neither ulcer over 2 cm.		

Comment. It is apparent from these results that the injection of glucose in a dose of 7.5 gm. per kilo divided into 2 doses during 24 hours did not influence the course of the experimental skin infection in rabbits. Such injections were continued for 6 days and, if anything, the trend in glucose-injected animals was toward more rapid healing of the skin. With increase of the dose of glucose to a total of 15 gm. per kilo divided into 6 doses during 24 hours, a marked increase in the extent of the skin infection was noted within 24 hours and often within 12. After the infection was well established in these animals, its advance was often evident grossly during a 4-hour period. In rabbits receiving similar amounts of 9% sodium chlorid intraperitoneally, the skin infection closely approximated that seen when glucose was used, indicating that a specific effect of glucose as such was not the chief factor involved. It would seem entirely probable that the changes observed were due to a disturbance in fluid balance in the animal. Whether or not a change in the fluid balance of the skin itself led to the marked decrease in its resistance to infection is not evident.

It is obvious that experiments involving frequent injections of a hypertonic solution are drastic and unphysiologic. In the initial experiments in which less frequent injections were given, the animals

only occasionally became toxic, with more or less severe diarrhea. In these animals, in spite of a total glucose dosage of 7.5 gm. per kilo in 24 hours, which in a 60 kilo man would represent an intake of 450 gm., no change in the course of the experimental infection was observed. It would seem that extreme and drastic conditions must be produced before the experimental skin infection is influenced greatly. All the animals receiving hypertonic glucose or sodium chlorid solution at frequent intervals eventually showed some evidence of toxicity, varying from slight listlessness to marked exhaustion. Moderate to severe diarrhea was always present and the urinary output was considerably increased. No direct correlation between the objective evidence of toxicity and the extent of the skin infection was noted; quite as commonly very toxic rabbits showed less evidence of skin infection than animals in which the injections were relatively well borne. In this connection we had the opportunity of observing several animals which contracted pneumonia shortly after the skin was infected. Although almost all the animals died, the extent and course of the skin infection was entirely comparable to that seen in normal rabbits.

Summary. The parenteral administration of glucose at 12-hour intervals in a dose of 7.5 gm. per kilo for a period of 6 days had no effect on an experimental staphylococcic skin infection in the rabbit.

When the dose of glucose was increased to a total of 15 gm. per kilo in 24 hours, given at intervals of 4 hours, a very marked increase in the extent of the experimental skin infection was noted (within 24 hours).

A similar effect was noted following injection of sodium chlorid solution of the same tonicity and in similar amounts.

An investigation of the effects of dehydration and acidosis on experimental skin infection is planned, as well as that of glucose administered by mouth.

We wish to acknowledge the valuable technical assistance of the Pepper Laboratory of the University Hospital in the bacteriological phase of this study.

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LYMPHOPATHIA VENEREUM.

(Lymphogranuloma Inguinale).

AND ITS RELATION TO RECTAL STRICTURE.

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THE cases of lymphopathia venereum considered in this communication were seen at the Pennsylvania Hospital during the past 2 years. The studies of DeWolf and VanCleve¹ and Cole² of Cleveland have brought this subject to the attention of the medical profession of this country. Sulzberger and Wise³ have suggested the name lymphopathia venereum. It is a less confusing and more accurate term than lymphogranuloma inguinale and we have adopted it.

Lymphopathia venereum is a chronic venereal disease, caused by a filterable virus.^{4,5} The transient and often herpetiform primary lesion of the skin is followed, in from 2 to 6 weeks, by the development of a characteristic subacute or chronic inflammatory reaction in the regional lymph nodes. Suppuration usually occurs; fistulas and sinus formation are common. The disease is primarily lympho-

tropic in nature. Rarely a localized cutaneous form is seen.^{6,7} Authentic extragenital cases have been recently reported.^{8,9}

In the early stages a constitutional reaction, of varying severity, may occur. It is rarely seen in temperate climates, where the disease seems to run a comparatively milder course. In the tropics and in the European countries chills, fever and leukocytosis are common, and erythema multiforme¹⁰ is often seen. Erythema nodosum was noted by Gans¹¹ in 10% of cases, usually occurring after operative interference in highly sensitized individuals. Meningeal symptoms, rheumatic manifestations¹² and enlarged spleen^{13,14} occasionally occur.

The disease probably occurs with equal frequency in both sexes, clinical variations being due to differences of the lymphatic drainage of the male and female. In the male the primary lesion is usually in the coronal sulcus. The infection passes up the penile lymphatics (occasionally causing a lymphangitis) and usually becomes localized in the inguinal glands. Rarely, because of the meager lymphatic channels, the iliac and hypogastric glands are involved. Although the intrapelvic glands are but rarely penetrated in the male, Bloom¹⁵ recently observed 3 cases of rectal stricture in men, out of a total of 7 cases. Elephantiasis of the male pudenda is occasionally seen.

The pathologic changes in the involved lymph nodes are probably not pathognomonic but are quite characteristic during the acute stages. They are not easily confused with tuberculosis, syphilis, Hodgkin's disease, sarcoma, or the more common infections of lymph nodes. The earliest change is the presence of multiple foci of epithelioid cells which may contain large giant cells. Many of these areas are transformed into micro-abscesses composed largely of neutrophils and large acidophilic mononuclear cells.¹⁶ These may coalesce to form larger abscesses. The normal structure of the node is lost as the involvement progresses. The process frequently spreads to the periglandular tissues and sinus formation (often multiple) occurs with drainage of the abscesses. Secondary infection is then frequent and chronicity is nearly the rule. In a number of our cases in which the involved nodes were excised at an early stage, the pathologist has ventured a diagnosis of lymphopathia venereum from the appearance of the microscopic picture (Fig. 1).

In from 2 to 6 weeks after the onset of the adenopathy, an allergic reactivity of the body tissues develops, which is demonstrable in nearly 100% of cases by the intradermal reaction of Frei.¹⁷ The antigen for this test is prepared from the pus obtained by aspiration of a bubo of a proven case of lymphopathia venereum. The technique for its preparation and administration is given in detail by DeWolf and VanCleve.¹ As the disease progresses the intensity of the reaction roughly parallels the severity of the involvement. In the latter manifestations, as will be pointed out in the present series, the reaction may decrease in intensity.

Frei believes that there are no false positive reactions. Cutaneous anergy occasionally occurs in active tuberculosis, in early florid syphilids, in high fever, in relapsing lymphopathia venereum lesions and sometimes in chancroid.¹⁸

In the female, inguinal adenitis is rarely seen, the virus usually passing to the intrapelvic glands. The anterior $\frac{2}{3}$ of the vulva is drained by the inguinal glands. The posterior $\frac{1}{3}$ is drained by the

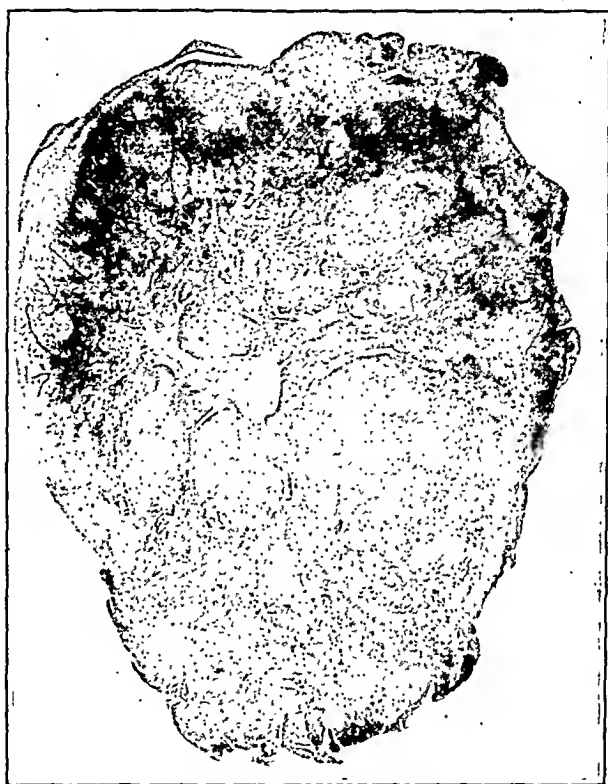


FIG. 1.—Low-power photomicrograph of an inguinal lymph node excised during the acute stage of involvement by lymphopathia venereum. Note the multiple abscesses of variable sizes. High-power examination shows the abscesses to be made up largely of neutrophils and mononuclear cells with acidophilic cytoplasm. At the borders of the abscesses, which are quite irregular, a hyperplasia of the reticulo-endothelial elements of the lymph node is evident and a number of giant cells are seen whose nuclei suggest reticuloendothelial origin.

intrapelvic glands, and there are extensive connections with the cutaneous lymphatic network of the anus. The vulvar and vaginal lymphatics have further ramifications to the anorectal glands, to those in the pouch of Douglas and to those lying in the broad ligament. The female, then, is subject not only to occasional inguinal involvement, but more commonly develops intrapelvic involvement with subsequent rectal stricture, perimetritis and perisalpingitis,¹⁹

esthiomene (vulvar elephantiasis), and perirectal granuloma and ulceration.

The exact pathogenesis of these later manifestations is not known. Frei believes that they are due to cicatricial contractions, to lymphatic blockage and to secondary infection. Barthels and Biberstein,²⁰ however, believe that active lymphopathia venereum is still present. They found a retrograde thrombotic lymphangitis with subsequent dilatation of the lymph spaces, characteristic stellate abscesses and inflammatory infiltrate. Their hypothesis of an attenuated virus has been in part proved by the recent experimental work of Ravaut.²¹

In the past a number of etiologic agents have been advanced as the causal factor in benign rectal stricture. Syphilis, tuberculosis, gonorrhea, chancroid and amebic dysentery have been most frequently suspected. The findings common to all of the large series of cases have been the high incidence of the condition in women (especially in the lower classes and the colored race), its occurrence during the period of greatest sexual activity (20 to 50 years), and the location of the stricture within a few centimeters of the anus.

In 1928 Frei and Koppel²² reported the presence of a positive Frei test in 5 cases of rectal stricture. One case occurring in a male showed evidence also of an old involvement of the inguinal lymph nodes. Following this report many observers confirmed their findings. In this country Cole² reported the presence of a positive Frei test in all of 15 cases of anorectal syndrome and esthiomene. Concomitant or preceding perirectal abscesses, fistulae and draining sinuses were frequent. In a series of 25 cases, all in negro women, Martin²³ noted a positive Frei test in 20 cases. Lee and Staley²⁴ in an excellent article on rectal stricture reported 16 cases of this condition (13 women and 3 men) 14 of whom had a positive Frei test.

The diagnosis in the male is usually easy. A positive Frei test is suggestive, but requires interpretation. Like the Wassermann reaction, it may be unrelated to the presenting lesion. Sarcoma, tuberculosis, gumma, lymphoblastoma and actinomycosis are most frequently confused. Specific treatment should be given if the Wassermann reaction is positive, but true cases of lymphopathia venereum often involute during antiluetic therapy.²⁵ Rectal stricture is rarely, if ever, syphilitic. Frei believes that it may occasionally be chancroidal or gonorrheal in origin.

Data. In this series 47 cases of lymphopathia venereum are presented, 22 males and 25 females. Forty (85%) were colored. These patients have been collected largely from the Out-patient Clinics, the annual total attendance of which approximates 22,500, with 37% colored. This suggests a much higher incidence of the disease in the colored race.

In 26 cases the disease was manifested by inguinal adenopathy. There were 22 males and 4 females; 22 colored and 4 white. The ages of the patients ranged from 17 to 45 years (average 25). The most common duration of the disease when first seen was from 2 to 4 weeks. Suppuration with sinus formation was rarely seen at this time. Four cases presented draining sinuses which had been present from 1 to 14 months. An evanescent primary lesion was seen on the penis in two instances. There was a history of a similar lesion in 1 other case. No clinical findings of chancroidal disease were found. Acute gonorrhcal urethritis and lymphopathia venereum occurred simultaneously in 1 patient. The 4 women presented no evidence of rectal stricture but typical vulvar elephantiasis (esthiomene) was present in one instance. A positive Wassermann and Kahn test was obtained in only 2 of the 26 cases.

The Frei test was positive in all of the cases of inguinal adenopathy. In 5 cases of inguinal adenitis secondary to chancroidal lesions, and 4 cases secondary to acute gonorrhcal urethritis, the Frei test was negative. It was negative also in 2 cases of granuloma inguinale, and 1 of reticulum cell sarcoma of the right groin.

There were 21 cases of rectal strictures, all occurring in the female, 18 in the colored race. The youngest patient was 19, the oldest 63 (average 37). The duration of symptoms when first seen, varied from 3 months to 9 years (average 4 years). The most frequent early symptom was an increasing constipation. Painful defecation, rectal bleeding, incontinence of feces, and discharges from the rectum were prominent features. In several cases there was a history of long standing draining sinuses about the anus. The location of the stricture was usually within 3 to 5 cm. of the external anal sphincter and within reach of the examining finger in all cases. This corresponds in location with the sites of the chief lymphatic networks about the anus and rectum (Fig. 2).

In 15 cases (71%) the Frei test was positive (strongly positive in 11 and moderately in 4). In the remaining 6 cases (29%) the Frei test was considered negative (there was a very slight reaction however in 3 of these 6 cases).

The Wassermann and Kahn tests were strongly positive in 5 of the 21 cases (23%). Four cases had both a positive Frei and a positive Wassermann reaction. Eleven cases had a positive Frei test and a negative Wassermann. Of the 6 cases with a negative Frei test, 1 had a positive Wassermann.

Three deaths occurred among the patients with rectal stricture. All of these cases had negative Frei tests. One case died as a result of a cerebral accident, followed by cardiac insufficiency and pneumonia. The blood Wassermann test was strongly positive, but at necropsy no pathologic evidence of syphilis was found. The rectal stricture began just inside the anus and extended upward a distance of 15 cm. The wall was fibrous and thickened and the mucosa was

congested. In some areas it was replaced by hemorrhagic granulation tissue.

In the second fatal case, death resulted from peritonitis which followed dilatation of the rectal stricture. At necropsy there was



FIG. 2.—Photograph of anus and rectum removed surgically in a case of benign rectal stricture. The patient was a colored woman aged 27. Increasing constipation with painful defecation had been present for 2 years. Bleeding from the rectum was frequent following straining at stool. A draining sinus which followed incision of a perirectal abscess, had been present for 6 months before removal. Clinically the stricture was located 4 cm. above the external anal sphincter and admitted only the tip of the forefinger. The Frei test was strongly positive (2 different antigens). Wassermann reaction was negative. The site of the stricture with ulceration of the mucosa of the lower rectum is evident. (Photograph after fixation which caused some shrinkage of the specimen.)

a large perirectal abscess, with extension upward along the left ureter to the perinephric tissues. The stricture was 5 cm. from the

external sphincter and associated with extensive ulceration of the rectum.

The third patient died also from a generalized peritonitis. Extreme emaciation and debility were present, with secondary anemia and typical skin lesions of pellagra. At necropsy the stricture was 3 cm. from the anus and extended upward a distance of 8 cm. Over this area, the mucosa was absent. The entire rectum and a portion of the sigmoid showed an acute ulcerative process, with the extension of the inflammation through the bowel wall to the peritoneal surface.

Microscopic sections from the stricture areas showed a marked fibroblastic proliferation with round-cell infiltration in all of these cases. In the latter 2 cases there was also acute inflammation present. In none was there evidence to suggest tuberculosis, syphilis or carcinoma associated with the stricture.

Treatment. There is no specific treatment for lymphopathia venereum. In those cases presenting inguinal adenitis surgical excision, Roentgen ray therapy and Frei antigen, intracutaneously, were all tried. Aspiration of the suppurating glands was frequently done when sinus formation was imminent. In a few cases incision and drainage were necessary. In general it seemed that sinus formation delayed recovery. Weekly injections of tartar emetic intravenously were used in several cases.

Three patients who failed to return for therapy were seen at a later date, and spontaneous regression of the inguinal adenitis had occurred without sinus formation. In view of this, and because of the poor follow up in the type of patient seen with this lesion, no conclusion can be drawn as to the results of therapy.

Tamura⁵ has recently reported cultivation of the virus on a medium of Tyrode's solution to which guinea-pig tissue had been added. When the culture was heated and used as an antigen for the Frei test it gave positive results in proven cases of lymphopathia venereum and negative results in normal individuals without this infection. The use of the virus culture in treatment as suggested by Tamura, would seem to be a step toward specific therapy in this disease.

The treatment of rectal strictures, when fully developed, is a surgical problem. It is doubtful if an active lymphopathia venereum infection is present in most of these cases, the stricture probably being the result of the healing process, with marked fibrous tissue proliferation. During the development of the stricture, which probably requires a number of years, non-surgical therapy may be of value as the lymphopathia venereum infection may be present in an attenuated form.

In 1 of the cases of this series, a colored woman, aged 27, symptoms has been present for 18 months. Painful defecation was present with frequent passage of small amounts of blood. Purulent

discharge from the anus was usually present. During this time she had 2 "boils" about the anus, which ruptured spontaneously and drained for an indefinite period. During several weeks preceding the time the patient was first seen, rectal pain had been a prominent feature, being present nearly continuously and interfering with sleep. Weight loss was striking. Inspection revealed a small drainage sinus lateral to the anus. Rectal examination was excruciatingly painful. The sphincters were very spastic and just inside the anus a stricture was present, which just admitted the forefinger. This was present as far as could be reached, and tender to palpation. A sanguinopurulent discharge was present following the examination.

Two Frei tests were strongly positive. The blood Wassermann test was negative. On the supposition that active infection was still present, tartar emetic was given intravenously. Relief from pain occurred within a few days. When examined 1 week later, the tenderness and spasm were greatly diminished. After 6 weekly injections of tartar emetic the patient was practically free from symptoms. Objectively the stricture was unchanged.

Comment. It is generally stated that the Frei test should be read after an interval of 48 hours. The possibility of a delayed positive reaction should be kept in mind. In 3 of the present series the Frei test did not become positive until after 72 hours. It would seem that the Frei test is best read on the 4th or 5th day. By this false positive reactions will have subsided.

In 4 instances of rectal stricture the Frei test was only moderately positive, in 3 there was a minimal reaction and in 3 there was no reaction (using 2 different antigens). It may be that in some of these long-standing cases there is a diminution in the intensity of the reaction and it is possible that the Frei test may occasionally become negative. On the other hand strongly positive reactions are often present many years after the infection has subsided. In those cases with a negative Frei test there was no history to suggest a previous gonorrheal or chancroidal infection. However, it is difficult to rule out these two infections as etiologic factors in the production of rectal stricture.

It would seem advisable that all cases of perirectal abscesses and fistulae in ano of unknown etiology should receive a Frei test. All contacts of cases in which the infection is active should be similarly tested.

The fact that the average age of the patients with rectal strictures was 37 years as compared to 25 years in those cases with inguinal adenopathy suggests that several years time is necessary for the development of the former lesion.

Summary. 1. Of 47 cases of lymphopathia venereum infection here reported, 26 presented inguinal adenopathy and 21 rectal stricture. One case was complicated by esthiomene.

2. Lymphopathia venereum occurs with much greater frequency in the colored race.

3. Reading the Frei test after the 4th day is recommended.

4. The possibility of a diminution or absence of the Frei reaction in long-standing cases is considered.

5. All patients with inguinal adenopathy of obscure etiology and those with rectal stricture should be tested with Frei antigen.

6. Cases presenting perirectal abscesses, fistulae in ano, or obscure pelvic infections should also be tested to eliminate the possibility of a lymphopathia venereum infection as an etiologic factor.

7. There is no specific treatment for the disease. Various methods have been considered.

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STUDIES IN HYPERTENSION.

1. THE PRODUCTION OF EXPERIMENTAL HYPERTENSION AND A CORRELATED EFFECT UPON THE NITROGEN DISTRIBUTION OF THE BLOOD PROTEINS.

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In a preliminary report¹ upon the production of experimental hypertension in rabbits by the injection of various substances, it was noted that of the amino acids employed, aspartic acid alone consistently produced hypertension. Our study has been continued using a large number of animals with the object of noting the effect of some of the supposed etiologic factors, which from clinical observation in man, are assumed to be associated with hypertension. No attempt will be made in the present paper to summarize, even briefly, the many views and experimental investigations on the problem of hypertension which the literature of the past quarter of a century records.

In accordance with the idea expressed above, chronic nephritis was produced in one group of animals; in another group the effect

of lipoids was observed and in a third the results of repeated injections of various amino acids was investigated.

Procedure. The following standard routine was adopted. Upon receipt of the rabbits, they were permitted to rest for 2 weeks. During this and for the entire period of observation, they were placed on a standard diet of carrots, oats and greens, such as beet tops, lettuce, etc. Blood pressure determinations were made 3 times weekly during the entire life of the animal, the method of McGregor² being employed, and 4 or 5 readings taken at each examination. The average of these readings was recorded. The diastolic pressure was not taken. The instrument used was a mercury manometer and all the readings were made by the same individual. It was found that after the animals had their pressures taken 2 or 3 times, they no longer became excited and remained perfectly quiet while restrained on the board. Urine examinations were made 3 times a week during the entire study and determinations of the blood urea nitrogen and creatinin were made during the 2 weeks control period and at intervals thereafter. All animals showing a systolic blood pressure of 120 mm. Hg or over during the control period were discarded.

Control Observations. In 66 normal rabbits the systolic blood pressure varied between 92 and 118 mm. Hg; in 19 (25.7%) the pressure varied between 92 and 100 mm., in 39 (59.1%) between 100 and 110 mm. and in 8 (15.1%) between 110 and 118 mm. Hg. In McGregor's² series of 84 normal rabbits, the averaged systolic blood pressure was 125 mm. Hg with a normal variation of 20 mm. Hg. In a number of control animals not included with the above mentioned 66 animals, spontaneous hypertension to a varying degree was observed. The observation period of the group was between 6 and 41 weeks and the actual rise of blood pressure varied between 24 and 49 mm. Hg.

Nephritis with Hypertension. Uranium nitrate was used to produce a nephritis, only 3 animals surviving sufficiently long to make the observations of any value. Two animals survived for 42 weeks. One animal received 88 doses of uranium nitrate, each dose being 0.7 mg., while the second received 84 doses of 0.58 mg. In both animals albumin and casts appeared in the urine and in both there was marked nitrogen retention in the blood, the blood urea nitrogen being 41.6 and 42.3 mg. per 100 cc. respectively. The blood pressure in the first animal rose from 110 to 132 mm. Hg and in the second from 108 to 155 mm. Hg. The third rabbit survived but 5 weeks and received 10 doses of 0.58 mg. of uranium nitrate. Albumin and casts appeared in the urine, the blood urea nitrogen rose to 63.3 mg. per 100 cc. and the blood pressure rose from 103 to 129 mm. Hg. Histologic examination of the viscera showed the usual picture of a uranium nephritis which was progressing to a chronic interstitial type. There was no evidence of vascular sclerosis.

It is evident, even in this small group, that a nephritis induced by repeated small doses of uranium nitrate causes an increase of the systolic blood pressure in rabbits.

Hypertension and Blood Lipoids. It has been maintained by some that hypercholesterolemia can be demonstrated in certain cases of hypertension and that there is an etiologic relationship. In accord-

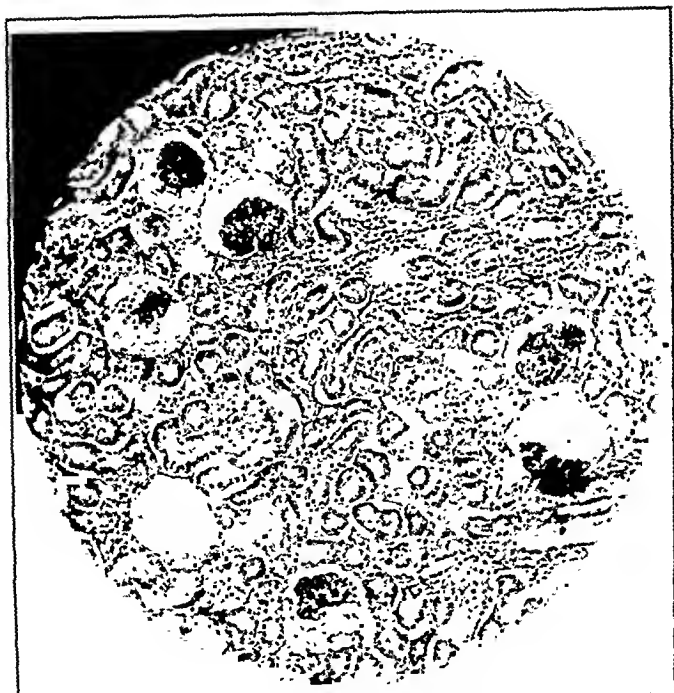


FIG. 1.—Glomerular nephritis after injection of aspartic acid.

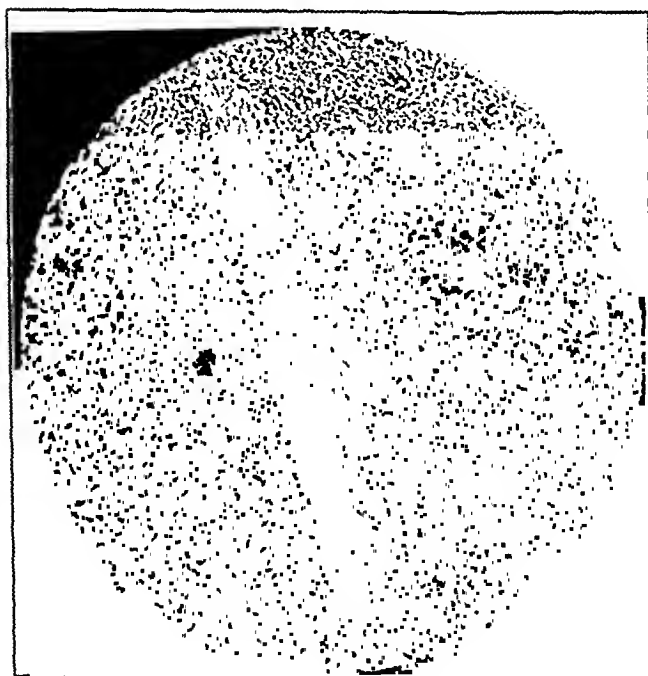


FIG. 2.—Splenitis after injection of aspartic acid.

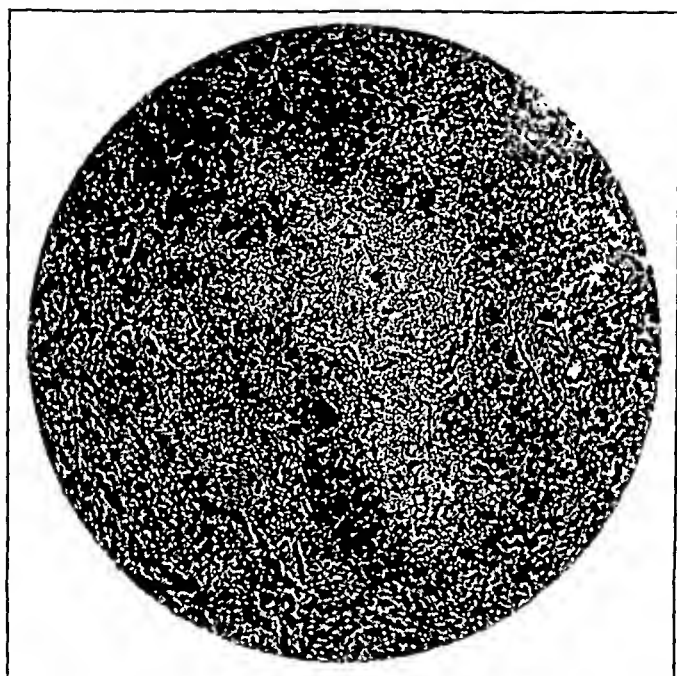


FIG. 3.—Spleen after injection of aspartic acid.

ance with this viewpoint a group of 7 rabbits were injected with repeated doses of cholesterol and 1 with a combination of cholesterol and lecithin. Of this group 5 animals survived.

The statistical data of the group are given in Table 1. With the exception of 1 animal, in which albumin and casts were found in the urine during the last month of life, no pathologic changes were observed in either the urine or blood.

As shown in Table 1, the repeated injection of cholesterol was followed by a mild degree of hypertension. In 1 animal when cholesterol and lecithin were combined, the hypertension did not develop. However, when the same quantity of cholesterol was administered alone to the animals, an increase in blood pressure was produced.

Since it has been shown that large doses of viosterol may upon occasion produce sclerotic changes in the vascular system, this substance was also tried, the data being grouped with the lipoids since chemically viosterol is a sterol (Table 1). It will be noted that a mild degree of hypertension did develop, always associated with kidney damage, but without nitrogen retention.

TABLE 1.—BLOOD PRESSURE IN CHOLESTEROL AND VIOSTEROL INJECTED RABBITS.

Animal No.	Period of observation (in weeks).	No. of doses.	Amount, mg.	Substance injected.	Blood pressure control period.	Blood pressure averages month by month.*
63	12	8	500	Cholesterol	109	128-130- 133
62	10	4	500	Cholesterol	116	133 -130-121
32	42	18	500	Cholesterol	111	116-128- 143 -138-141-138-136-124-123-114
61	34	7	500	Cholesterol	117	140 -136-131-134-121-112-111-103
			100	Lecithin		
88	23	61	200	Cholesterol	99	113- 116 -107-100-100-102
42	5	25	1 cc.	Viosterol 250 D	107	113
43	10	45	1 cc.	Viosterol 250 D	99	100-109-100
44	31	99	1 cc.	Viosterol 250 D	108	108-112-118-124- 126 -115-118-112
45	23	96	1 cc.	Viosterol 250 D	97	105-115-125-130-130

* The highest pressure obtained is in bold type.

Protein Putrefaction Products. Two protein putrefaction products, putrescin and tyramin, were used in another group of rabbits. Only 2 animals survived sufficiently long to make the observations of any value. One animal during 27 weeks received 86 injections of 100 mg. each of putrescin. The lowest blood pressure recorded was 105, the highest 123. The second animal during 11 weeks received 60 injections of 50 mg. each of tyramin. The lowest blood pressure recorded was 107 and the highest 110. In both animals the urine and blood chemistry were normal.

As far as can be judged from these few observations, it seems that neither putrescin nor tyramin when injected into rabbits produce any rise in blood pressure.

Amino Acids. In another group of animals various amino acids were injected. Since many of the experimental results were negative and the survivors few, the statistical data are given without comment (Table 2).

TABLE 2.—BLOOD PRESSURE AFTER INJECTION OF AMINO ACIDS.

Period of observation (in weeks).	Substance injected.	Number and amount per injection.	Blood pressure.	
			Minimum.	Maximum.
10	Histidin	40-100 mg.	107	113
23	Tryptophane	29-200 mg.	106	121
27	Tyrosin	51-100 mg.	105	115
33	Asparagin	82-200 mg.	112	121
33	Asparagin	{ 28-240 mg. 46-200 mg. }	108	122
19	Asparagin	40-200 mg.	104	134
18	Glutamic acid	94-500	109	122
17	Glutamic acid	44-100	105	129
44	Glutamic acid	117-100	122	141

Aspartic Acid. Since it is in this group that a significant increase in blood pressure was found, detailed discussion of all of the 11 surviving animals will be presented (Table 3).

In practically all of the animals of this group, albumin and casts appeared in the urine within 4 to 6 weeks after the first injection. The amount of albumin was never more than a faint trace and in none of the animals was there nitrogen retention in the blood. This is analogous to the condition commonly found in essential hypertension in man, where the only symptoms often are increased blood pressure with or without albuminuria and no nitrogen retention in the blood.

At autopsy the kidney lesion found in these animals was that of a glomerular nephritis with congestion of the tufts and an exudate in the glomerular space (Fig. 1). If one were to express the extent of the lesion mathematically, it would be in the general order of one glomerulus out of 15.

In the spleen a series of changes occurred which led to almost complete fibrosis of the organ. In extreme cases the usual histology of the organ was completely replaced by a mass of hyalin connective tissue, in which small foci of round-cell infiltration were demonstrable. For the greater part the sinuses were still preserved, though the lymphoid structures were completely destroyed. The best histologic description of the advanced stages is that the sections could not be recognized as spleen. These changes in the rabbit spleen have their counterpart in man, where in cases of hypertension chronic splenitis in varying degrees is also observed, none, however, as extensive as that observed in the rabbit. The condition of the spleen is shown in Figures 2 and 3.

Sections of the great vessels showed no definite histologic change, except for a possible increased prominence of the elastic fibers and occasional areas of vacuolization in the media. There were two exceptions: Rabbit 87 showed definite calcified areas in the aorta, and Rabbit 33 showed marked sclerosis of the tibial vessels associated with gangrene of all the toes on the hind legs leading to spontaneous amputation.

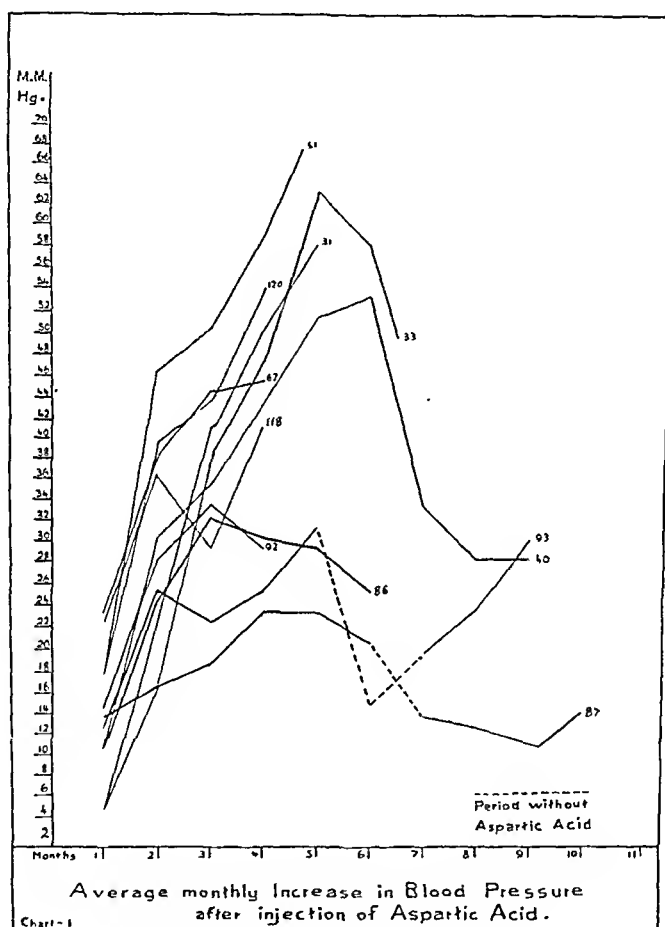


CHART I.

The blood pressure of the rabbits injected with aspartic acid showed a definite continuous rise from month to month in practically all of the animals (Chart I). The rise was more marked in some animals than in others. Allowing for seasonal variations, similar changes were not observed in the control animals, nor in animals injected with other substances. While the period of observation extended from 4 to 21 months, the data for only 10 months is shown graphically. The rise in pressure is slow, increasing from 4 to 23 mm. Hg in the first month. The maximum increase was

obtained in 2 animals in 3 months, in 3 animals in 4 months, in 5 animals between 4 and 5 months and in 1 animal in 6 months.

When injections of aspartic acid were temporarily discontinued for a period, as in Animals 87, 93 and 40, there was a definite decline in the blood pressure, but upon resumption of the injections the pressure resumed its upward trend.

Having noted that the repeated injections of aspartic acid produced a rise in blood pressure, the more immediate effects of a single injection were studied in 2 instances. The blood pressure was taken 1, 6 and 24 hours after an injection of 500 mg. The increase in blood pressure of the first animal at the designated intervals was 6, 12 and 6 mm. Hg, and in the second animal it was 4, 2 and at the last interval a drop of 8 mm. Hg below the original level. These changes are within normal limits of variation and can be discarded.

In Chart II we have plotted the blood pressure curves of Rabbits 87 and 40 week by week for the entire period of observation.

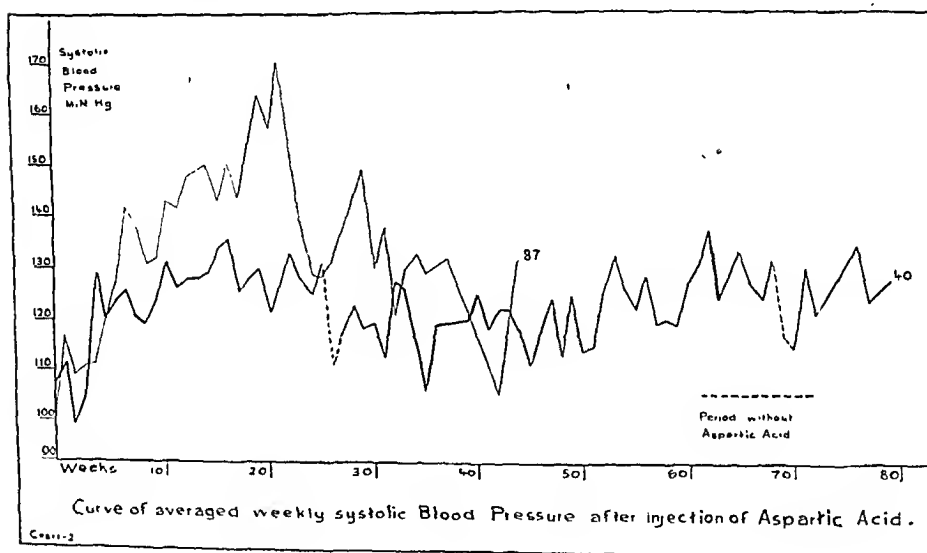


CHART II.

Guanidin Carbonate. Major³ and his coworkers have reported an increase of guanidin in the blood in cases of hypertension in man. This substance was injected into another group of rabbits, of which 5 survived. In all of the animals a nephritis of varying severity was found postmortem, and during life albumin and casts were found in the urine. There was no evidence of nitrogen retention in the blood.

This group of animals was under observation from 6 to 26 weeks. The control blood pressures varied between 94 and 117 mm. Hg. All of the animals received between 13 and 32 injections of 200 mg. of guanidin carbonate and the maximum blood pressure during the experimental period ranged between 129 and 172 mm. Hg.

A similar type of fibrosis of the spleen observed in the aspartic acid hypertension was also noted in this group.

It is evident that injections of guanidin carbonate are followed by the development of hypertension. Attention is called to the fact that guanidin carbonate is toxic and gangrenous areas developed at the site of injection. The periods of observation were short due to the high mortality, as compared to the aspartic acid group.

Succinic Acid. In this group 3 animals survived; diarrhea and abscesses at the site of injection were common. The blood pressure before injection varied between 100 and 103 mm. Hg. They were under observation from 15 to 36 weeks. One animal received 115 injections of 50 mg. of succinic acid, the second 37 injections of 100 mg., and the third 135 injections of 100 mg. The rise in blood pressure during the experimental period was not sufficient to be of significance.

In all of the animals a nephritis of slight severity was observed postmortem, and during life all showed albumin and casts. There was no nitrogen retention in the blood. A slight fibrosis of the spleen was also observed.

The injection of succinic acid into rabbits does not produce hypertension.

Nitrogen Distribution of the Blood Proteins. As part of the investigation, a study of the nitrogen distribution of the blood proteins of normal and hypertensive rabbits was undertaken, the results of which are recorded in this paper. The examinations deal with the distribution of the total, the amid, the hydrolyzable, the basic amino and the monoamino nitrogen of the whole blood, of the red cells and of the serum proteins from the same specimen of blood in normal rabbits and those made hypertensive by the repeated injections of aspartic acid.

All of the blood specimens were obtained in the morning, all food having been removed from the cages the previous evening. The technical methods for the analysis of the blood proteins have been described in detail.^{4,5}

Normal Values: Table 4 records the total, the amid, the hydrolyzable, the basic amino and the monoamino nitrogen of the whole blood, red cells and serum proteins of 17 normal rabbits. To conserve space, only the high, low and the average for each of the constituents are given. The animals varied in weight from 1507 to 2755 gm.

Special attention is directed to the serum proteins and emphasis is placed on the basic amino (subsequently termed B.A.N.) and monoamino nitrogen (subsequently referred to as M.A.N.). We have proposed a ratio of the monoamino and the basic amino nitrogen which will be referred to throughout this paper as the *M/B* ratio.

Changes in the amid nitrogen are of no significance. Neither this

fraction nor the humin nitrogen play a rôle in the results obtained since both are removed before the other fractions are determined. The humin nitrogen has not been reported in the tables. Reference to these two fractions will, therefore, be omitted from the discussion.

TABLE 4.—NITROGEN DISTRIBUTION OF THE WHOLE BLOOD, RED CELLS AND SERUM PROTEINS IN 17 NORMAL RABBITS.

	Total N.	Amid N.	Total N ¹ after hydrolysis.	Basic amino N.	Total N. % after hydrolysis.	Total N. of phosphotungstic acid filtrate.	Mono-amino N.	Total N. % after hydrolysis.	M/B ratio.
				Milligrams per 100 cc.					
				Whole blood					
High	2670	220	2420	700	31	1770	1620	76	4.2
Low	2005	60	1560	360	17	1160	1000	54	1.8
Average	2391	107	2060	535	25	1520	1340	65	2.6
				Red blood cells					
High	2040	140	1870	530	34	1350	1220	74	4.2
Low	970	30	700	160	18	850	740	48	1.6
Average	1717	86	1491	409	27	1096	959	65	2.5
				Serum proteins					
High	900	80	670	170	25	510	500	82	5.5
Low	570	17	460	90	15	340	270	47	2.3
Average	669	27	548	117	21	428	370	66	3.2

¹ After removal of humin and amid nitrogen.

In normal rabbits the basic amino nitrogen of the serum proteins varied between 90 and 170 mg. with an average of 117 mg., forming between 15 and 25% with an average of 21% of the total nitrogen after hydrolysis. The monoamino nitrogen varied between 270 and 500 mg. with an average of 370 mg. per 100 cc. The percent which this fraction formed of the total nitrogen after hydrolysis varied between 47 and 82 with an average of 66. The M/B ratio varied between 2.3 and 5.5 with an average of 2.3. In 16 rabbits the ratio varied between 2.3 and 3.9 and in only 1 animal was the ratio at the high point of the extremes.

Nitrogen Distribution in Hypertension. Since significant changes occur in the serum proteins of hypertensive animals, discussion will be confined entirely to this fraction. The data presented in Table 5 shows the nitrogen distribution of the serum proteins of rabbits before and after the production of hypertension with aspartic acid and guanidin carbonate. A more detailed discussion of some of the results follows.

Protocols. Rabbit 92. During the control period the blood pressure was 102. (In the following portions of the report, mm. of Hg will be omitted from the blood pressure values and mg. per 100 cc. will be omitted after the values of the various nitrogen fractions. The percentage values in parenthesis indicate the percentage of that particular fraction of the total nitrogen after hydrolysis.) At the same period the B.A.N. was 90 which

TABLE 5.—NITROGEN DISTRIBUTION OF THE SERUM PROTEINS IN RABBITS WITH HYPERTENSION.

Rabbit.	Blood pressure.	Total N.	Amid N.	Total* N. after hydrolysis.	Basic amino N.	Total N. after hydrolysis.	Total N. of phosphotungstic acid filtrate.	Mono amino N.	Total N. % after hydrolysis.	M/B ratio.	Substance injected.
	Min.	Milligrams per 100 cc.					Milligrams per 100 cc				
92	102	801	25	900	90	15.0	500	490	82.0	5.5	Control
92	130	610	20	590	33	5.6	550	530	90.0	16.0	Aspartic acid.
93	90	620	21	510	110	20.4	450	400	74.0	3.6	Control.
93	130	530	20	470	40	8.5	430	450	95.0	11.2	Aspartic acid.
93	130	850	21	930	30	4.7	600	600	95.2	20.0	Aspartic acid.
93	114	680	27	510	140	27.4	370	300	60.0	2.1	Aspartic acid. discontinued 3 weeks.
118	105	650	30	530	130	24.5	400	370	70.0	2.8	Control.
118	130	600	10	570	70	12.2	500	500	88.0	7.1	Aspartic acid.
120	102	610	20	530	130	23.6	420	420	70.0	3.2	Control.
120	144	620	20	490	70	14.3	420	420	86.0	6.0	Aspartic acid.
98	104	900	22	530	130	24.7	400	300	55.5	2.3	Control.
98	128	780	22	390	40	10.0	350	310	87.0	8.4	Guanidin carbonate.
103	106	800	40	500	100	20.0	400	350	70.0	3.5	Control.
103	136	800	40	500	70	14.0	440	350	70.0	5.0	Guanidin carbonate.
103	118	810	40	710	140	20.0	570	300	42.0	2.1	Guanidin carbonate discontinued 1 month.

* After removal of humin and amid N.

represented 15% of the total nitrogen after hydrolysis, the M.A.N. was 490 (82%) and the M/B ratio was 5.5. The blood pressure reached a maximum of 150, a rise of 48, 106 days after the first injection of aspartic acid. During this period 78 injections of 500 mg. of aspartic acid were given. Five days later the pressure was 130 and on that day the serum proteins were B.A.N. 33 (5.6%), M.A.N. 590 (90%), and the M/B ratio 16.0. During the period of hypertension a change in the distribution of the nitrogen fraction had occurred. The important change is a decrease in the B.A.N. and an increase in the M.A.N. with a consequent rise in the M/B ratio. Attention is called to this fact since exactly similar changes have been observed in a group of cases of hypertension in man and will be reported in a subsequent paper.

Rabbit 93. During the control period this animal had a blood pressure of 90 and the B.A.N. was 110 (20.4%), the M.A.N. 400 (74%), and the M/B ratio 3.6. After 79 injections of 500 mg. of aspartic acid in 108 days the blood pressure rose to 130. At this time the B.A.N. was 40 (8.5%), the M.A.N. 450 (96%) and the M/B ratio 11.2. Sixteen injections of 500 mg. of aspartic acid were given in the ensuing 35 days, the blood pressure rising to 144. The B.A.N. was 30 (4.7%), the M.A.N. 600 (92.5%) and the M/B ratio 20.

Injections of aspartic acid were discontinued for 25 days, at the end of which time the blood pressure was 114. At the same interval the B.A.N. rose to 140 (27.4%), the M.A.N. fell to 300 (60%) and the M/B ratio fell to 2.1. The results in this instance demonstrated that blood pressure, monoamino nitrogen and the M/B ratio rose after the repeated injections of aspartic acid and that a discontinuance of the injections was followed by a more or less complete return to the normal.

Rabbit 118. During the control period the blood pressure was 105, the B.A.N. 130 (24.5%), the M.A.N. 370 (70%) and the M/B ratio 2.8. Over a period of 64 days, 24 injections of 500 mg. of aspartic acid were given with blood pressure to 152. Some days later the blood pressure had fallen to 130 and the B.A.N. was 70 (12.2%), the M.A.N. 500 (88%) and the M/B ratio 7.1.

Rabbit 120. During the control period the blood pressure was 102, the B.A.N. 130 (23.6%), the M.A.N. 420 (76%) and the M/B ratio 3.2. In 63 days this animal received 12 injections of 500 mg. of aspartic acid. The blood pressure was then 144, the B.A.N. 70 (14.3%), the M.A.N. 420 (86%) and the M/B ratio 6.0. In this animal there was no actual increase in the amount of monoamino nitrogen, but the percentage of this fraction of the total nitrogen after hydrolysis was increased. The rise in the M/B ratio was due to a fall in the B.A.N.

Rabbit 98 was observed for 6 weeks, receiving 24 injections of 200 mg. of guanidin carbonate. During the control period, the blood pressure was 104, the B.A.N. 130 (24.7%), the M.A.N. 300 (55%) and the M/B ratio was 2.3. Forty days after the first injection the blood pressure was 152, the B.A.N. 40 (10%), the M.A.N. 340 (87%) and the M/B ratio 8.4.

Rabbit 103. This animal was observed for 20 weeks and received 21 injections of 200 mg. of guanidin carbonate. During the control period the blood pressure was 106, the B.A.N. 100 (20%), the M.A.N. 350 (70%) and the M/B ratio 3.5. When the pressure had risen to 136, the B.A.N. was 70 (14%), the M.A.N. did not change, but the M/B ratio was 5. The injections were discontinued and 4 weeks later all of the nitrogen values and the M/B ratio were within normal limits.

Discussion. Clinical observation has indicated a relationship between hypertension and a variety of clinical entities; thus, chronic nephritis, chronic lead poisoning, syphilis and the excessive use of

alcohol are commonly regarded as important etiologic factors. There are also other conditions which are supposed to initiate or to keep the process in continuance and it seems logical to suppose that all these agents act through a common mechanism. It is also evident that this mechanism is intrinsic rather than extrinsic. Many have assumed that hypertension is due to a disturbance of metabolism, although just what processes are involved have never been definitely shown. The physiologic action of amino acids resulting from catabolism of proteins, or products resulting from failure of the organism to properly deaminate amino acids, might play some rôle in hypertension. It has been shown by the present experiments that aspartic acid, one of the normally existing amino acids in the organism, when repeatedly injected into rabbits produces hypertension and glomerulonephritis. This effect is not due solely to the presence of the amino group, since the injection of other amino acids does not produce hypertension. Glutamic acid which is closely related chemically to aspartic acid does not raise blood pressure. Aspartic acid and glutamic acid are two common mono-amino dicarboxylic acids and differ from each other by one methyl group.

Deamination of amino acids is a property of a great many tissues of the body and it is probable that certain of them possess a selective action in this respect. Under normal conditions, presumably all of the amino acids in excess of the required nitrogenous structural units are deaminized, yet it is possible that with a perfectly normal mechanism for deamination, the organs cannot deaminize the aspartic acid at the rate at which it accumulates and there is an excess which is sufficient to cause an elevation of blood pressure. Deamination of aspartic acid results in the formation of succinic acid. Our experiments indicate that succinic acid plays no rôle in the production of hypertension.

The exact mechanism by which the blood proteins are formed from ingested amino acids is not entirely known and it is likely that the presence of a large quantity of any particular amino acid might alter the composition of the proteins, with resultant changes in their physical and chemical properties. In rabbits developing hypertension after the administration of aspartic acid, changes in the nitrogen distribution of the serum proteins occur. These changes are a lowering of the basic amino nitrogen values and an increase in the monoamino nitrogen fraction, in consequence of which there is a rise in the M/B ratio. Aspartic acid and glutamic acid are the principal amino acids which constitute the monoamino nitrogen fraction of the serum proteins. Since glutamic acid plays no rôle in the production of hypertension, it seems logical to assume that aspartic acid is the responsible factor.

Guanidin carbonate is not an amino acid, but it also is a hypertension producing agent, inducing changes in the nitrogen fractions

of the serum proteins of the same character as that observed after the injections of aspartic acid. In the guanidin animals the changes are more pronounced in the basic amino nitrogen fraction with little or no change in the monoamino nitrogen fraction. The M/B ratio of the guanidin injected animals is not as high as those of the aspartic acid group.

Conclusion. 1. Uranium nitrate when injected in small doses into rabbits produces nephritis with hypertension.

2. Cholesterol similarly administered produced a mild hypertension, while in a single experiment cholesterol and lecithin did not.

3. Of the amino acids injected, aspartic acid alone produces definite hypertension. At autopsy, the renal lesions of glomerulonephritis were found.

4. The aspartic acid hypertension in rabbits is not dependent upon the presence of the amino or dicarboxylic group.

5. Guanidin carbonate also produces hypertension when injected into rabbits.

6. A marked fibrosis of the spleen was observed in all of the animals which developed hypertension after the injection of aspartic acid.

7. The total, the amid, the hydrolyzable, the basic amino and the monoamino nitrogen distribution of the whole blood, of the red cells and of the serum proteins from the same specimen of blood have been determined in 17 normal rabbits and in 6 rabbits with hypertension.

8. In rabbits in which hypertension has been produced by the injection of aspartic acid, the basic amino nitrogen fraction of the serum proteins is decreased, the monoamino nitrogen fraction is increased and there is a rise in the M/B ratio.

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HEREDITARY ONYCHIAL DYSPLASIA.

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THE anomaly presented in this article is not common, if a review of the literature may indicate its frequency. Nevertheless the subject is of unusual interest, and thus far, there seems to be no agreement as to the explanation of the method of inheritance in this syndrome. One might even gather that various writers were presenting different syndromes. Such, I feel, is not the case, and the most recent paper of Asehner,¹ in which an attempt is made to advance the theory that chance linkage of separate factors accounts for the syndrome, does not seem to offer an adequate solution to the problem.

Realizing the difficulties in explaining the genesis of this syndrome, the writer has presented the views of MacArthur,^{2,7} with which he agrees, as the basis for much of the discussion which follows.

A case is presented as a typical example. The patient was admitted to hospital as a diagnostic problem. The history, other than dealing with the syndrome presented, will be but briefly mentioned.

Case Report.—G. S., a white male, aged 29, fisherman, English, single, was admitted to hospital on July 18, 1934, complaining of cough, and sputum. His past history was irrelevant. His family history was negative except for the peculiar dystrophy of nails which occurred in several instances. One female cousin is a patient in a hospital for mental diseases, who also shows the nail dystrophy. The functional inquiry was negative except for cough and sputum.

Physical examination showed few positive findings. The patient was intelligent, and cooperated well. He was well developed. The skin was normal over the whole body, except for scales over the elbows and knees, as one would expect to find in a salt-water fisherman. There was no obvious postural deformity, nor external evidence of any glandular disturbance. The hair was plentiful, and of medium texture; the scalp was clean. The eyes, ears, nose, mouth and throat were normal. The thyroid gland was normal in size and consistency. The trachea was in the midline. The right lung was normal. The left lung exhibited medium râles below the 6th rib, anteriorly, and the 9th rib, posteriorly, along with some dullness to percussion. There was nothing abnormal in the entire cardiovascular system. The systolic blood pressure was 110 mm. Hg, diastolic, 60. The abdominal muscular development was pronounced. There was a slight inguinal hernia on the left side. The genitalia were normal. The extremities showed no abnormal protuberances. The patellæ were normal in size and position. There was normal movement in all joints. The fingers and toes showed peculiar distribution of the nail substances (Figs. 4 and 5). The nail deficiency was most marked on the thumbs and great toes. These findings are very similar to those previously reported, and almost identical

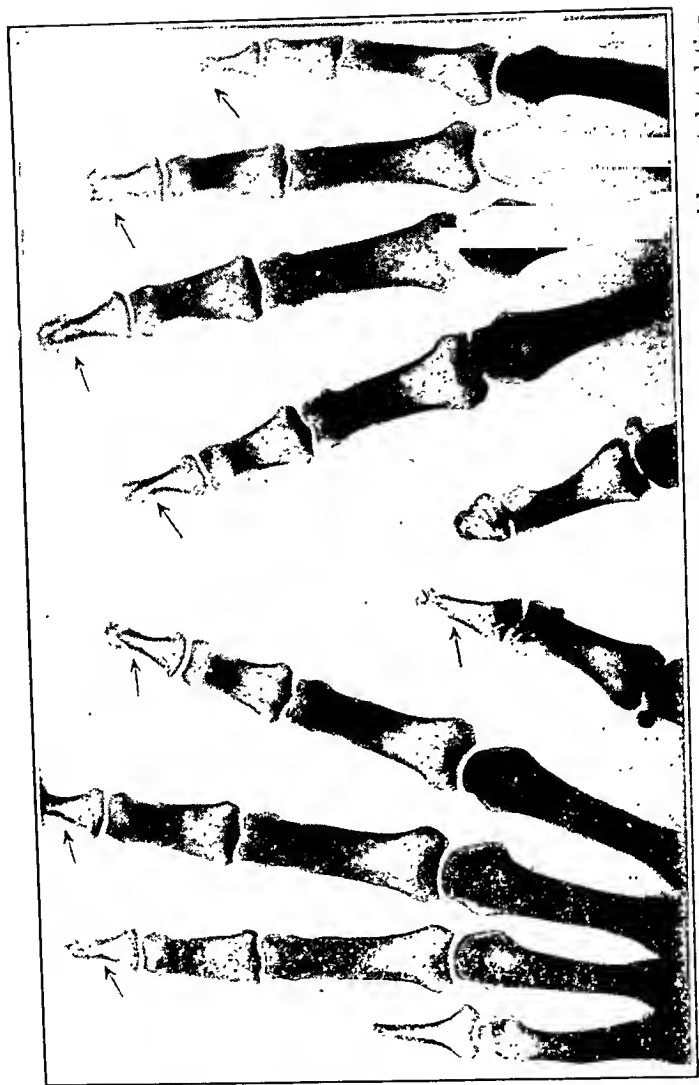


FIG. 1.—Roentgen ray of hands shows unusual tapering of distal phalanges with spatulated tips. Arrows are drawn to show the changes. Injuries to the distal phalynx of thumb on right hand and little finger on left hand are evident. (Roentgen ray read by Dr. S. Kirkland, roentgenologist, Saint John General Hospital.)

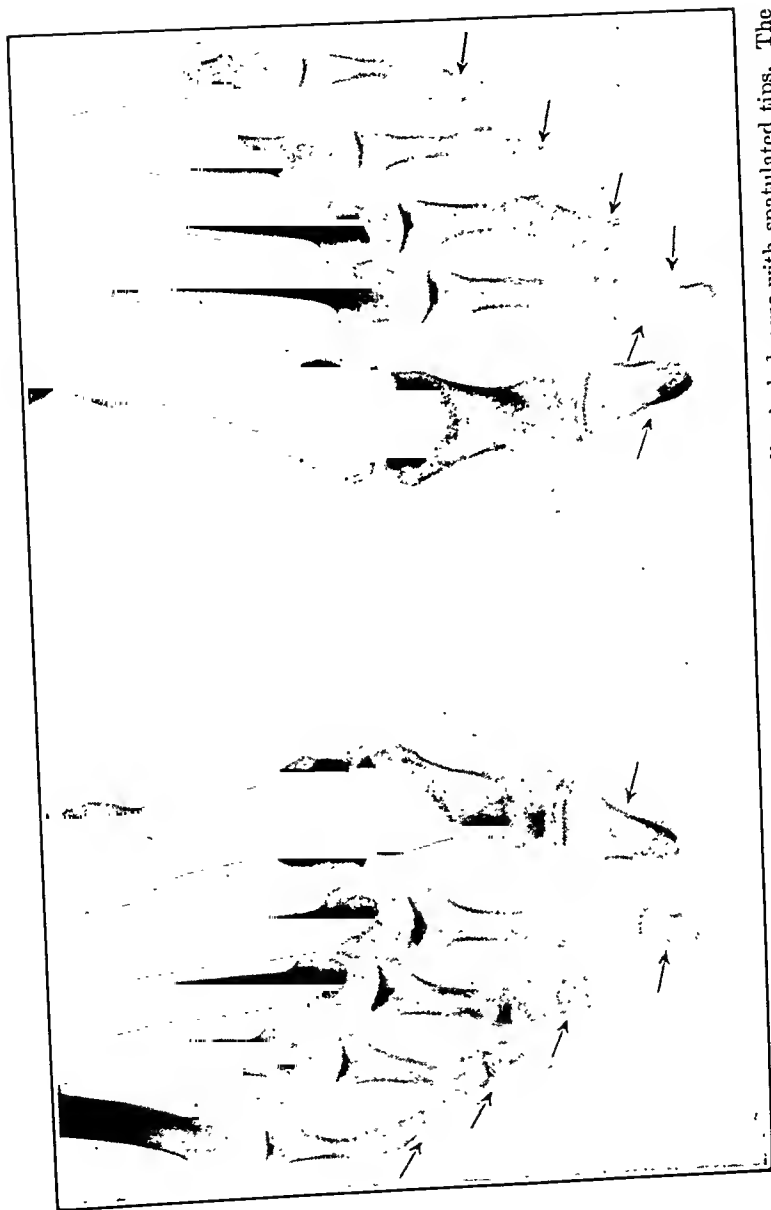


FIG. 2.—Roentgen ray of feet. There is unusual tapering of the distal phalanges with spatulated tips. The arrows drawn point out the defects. (Roentgen ray read by Dr. S. Kirkland, roentgenologist, Saint John General Hospital.)

with that of the female cousin mentioned. The spine and nervous system showed no abnormalities.

Laboratory data were as follows: Urine, normal. Blood, red blood cells, 5,730,000 per c.mm., with 88% hemoglobin; the white blood cells were 5000 per c.mm., with neutrophils 53%, eosinophils 2, lymphocytes 38, and monocytes 7. The blood Wassermann and Kahn tests were negative.



FIG. 3.—Roentgen ray of dorsal spine. This shows lateral wedging of the ninth dorsal vertebra, with some slight changes from normal in several other bodies (see arrows). (Roentgen ray read by Dr. S. Kirkland, roentgenologist, Saint John General Hospital.)

Roentgen ray of chest showed evidence of some bronchiectasis at the base of the left lung. Practically the entire skeleton was Roentgen rayed. This revealed some slight abnormalities of the hands, feet and dorsal vertebrae. The distal phalanges of the hands and feet were tapered and spatulated (Figs. 1 and 2). Lateral wedging of the dorsal vertebrae was also

evident (Fig. 3). The gradation of nail dystrophy is shown in photographs (Figs. 4 and 5).

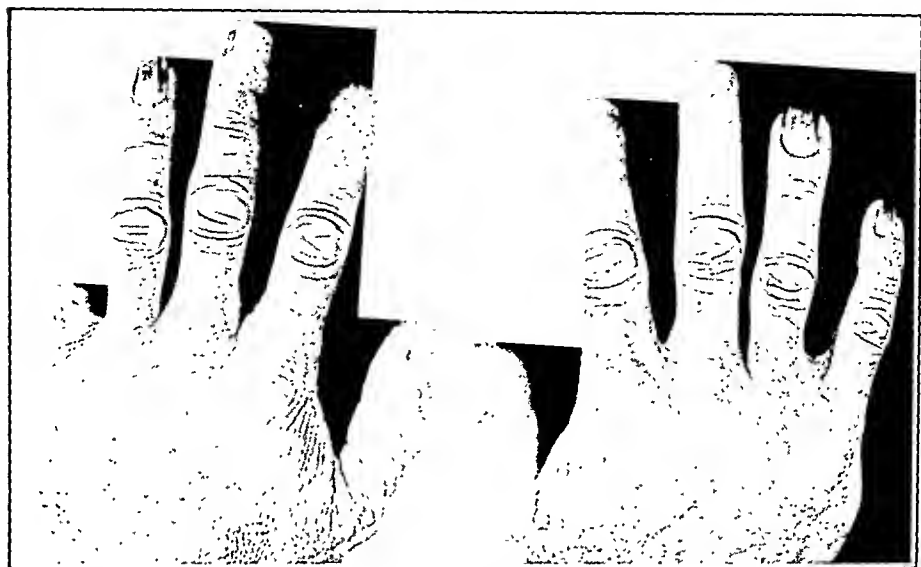


FIG. 4.—Photograph of hands of G. S. The gradation of nail dystrophy is shown. There is no normal nail substance present. Thickening with heaping up and longitudinal furrowing is present. The shortening of the thumb on the right hand and little finger on the left hand are due to injuries.

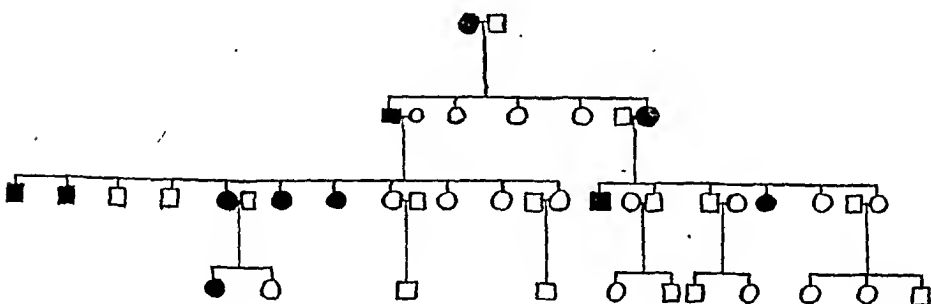
Discussion. The family tree (Chart I) is composed of 35 members among whom nail dystrophy occurred in 11 instances. Unfortunately G. S., and a female cousin, mentally deficient, were the only



FIG. 5.—Photograph of feet of G. S. The distribution of nail substance is much the same as shown in the hands. No nails are normal.

individuals examined. Arrangements could not be made to get Roentgen films of the latter. The others were reached by a ques-

tionnaire, worded to reveal obvious defects such as alopecia, ichthyosis, absence of sweat glands, etc. Dystrophy of the nails was the only ectodermal abnormality reported, although the changes noted varied considerably. Several had difficulty in picking up small objects, due to lack of nail substance. No skeletal deformities were noted, and those present in G. S. were unlike any previously reported. Hypothyroidism has been suggested as a causative factor but no evidence of this was found in any member. As it is unlikely that this factor is of any importance in this syndrome, a basal metabolic rate was not done. One case of mental disease occurred in this family, but no conclusions can be drawn from this fact. The defects occurred in approximately one-half to one-third of the number of children whose parent was affected, and in no instance did an un-



Key.

☐ Normal male.

○ Normal female.

■ Affected male.

● Affected female.

CHART I.—Family tree. There are 35 members. The symbols indicate nail dystrophy.

affected parent transmit a defect. Both sexes were equally affected. These findings are substantiated by those of Tobias,³ Jacobson,⁴ Thompson,⁵ and Turner.⁶ No marriage occurred between 2 affected individuals, nor have any such been reported. Consequently all cases are probably heterozygous (Dd). The possibility should be kept in mind that if any (DD) progeny, they might be lethally affected. It is safer then to admit that the gene (D) may not be dominant as at first seems probable.

Hereditary dystrophy of the nails has been reported associated with ectodermal and mesodermal defects and as an entity. Many had no Roentgen rays taken, and anomalies of the osseous system have undoubtedly been missed, as deformities are often revealed by this examination alone. The case presented here is an example of this. The gradation of nail dystrophy and other ectodermal and

mesodermal defects reported have varied greatly. It is probable that in most cases, at least 2, and possibly all three primary body layers are affected in this syndrome. Endodermal structures inaccessible to examination may also be involved. It is likely that the many clinical pictures met with are merely variations of the same disease. The case presented here is an example of the minor effects of the syndrome, while those showing such defects as absence of the patellæ, subluxation of the radius, etc., illustrate its more serious forms. If this assumption is correct, a satisfactory explanation of the genesis of this syndrome has not appeared thus far. The associated characters of the syndrome; the difference in its make-up in different families; its frequent dissociation, and its great variability among individuals are the chief unsolved genetic problems. Previous writers have attempted to account for these peculiar hereditary features by assuming either one or more modifying genes (Turner⁶), or separate genes for each of the associated defects noted, such as dystrophy of the sweat glands, hair, patellæ, etc. It is assumed that the genes come together by chance association as in Mendelian polyhybrids, or are held together by linkage in one chromosome (Aschner¹).

Against the theory which states that each single component of the group of characters has its own separate cause, MacArthur² notes the following objections: "If the genes assort freely, they cannot produce the correlation observed between the elements of the syndrome; if they are linked, as Aschner maintains, they would tend to go together and produce a correlation, high or low, according to the closeness of the linkage, that might last for generations; but this apparently attractive view encounters serious difficulties; (1) when the syndrome first appeared, the several genes controlling it, must all have chanced to mutate at about the same time, and (2) all have happened to lie in the same chromosome, and (3) most of them to affect similar parts (*e. g.*, skin or ectodermal derivatives) whereas genes appear actually to be distributed at random on the chromosome and to mutate singly and at random in the set.

"It is probable that the components of the syndrome which are generally inherited together also originated together. Accordingly, it would seem best to reject for the present the linkage theory, at least in the form presented, as a much less satisfactory explanation of the syndrome than the simpler alternative theory that the whole syndrome arises from a *common* fundamental cause tracing mainly to the differential effects of one gene. In a disease syndrome the associated symptoms commonly arise together, or are traceable to one early starting point, one cause leading to other succeeding effects in train. Analogously, it is an accepted fact that a gene typically exhibits a variety of effects; such diverse effects are probably what are observed in a syndrome."

It has already been shown in the work of MacArthur⁷ and

Landauer,⁸ that certain syndromes can be plausibly pictured and reasonably explained as arising developmentally, and due to the multiple effects of a gene. "Since gene action is evidently not entirely localized and specific but may reach various, often dissimilar, parts and structures and derivatives even of different germ layers, it may be viewed as operating in a more or less specific way as regards time and rate, producing for instance a retardation of development, acting over a limited period, during which parts capable of responding to its influence are in process of being developed and fixed. The parts most actively developing during the time of action of the gene are most affected; structures once fully developed are not further alterable. Variations of the syndrome would on this view be due either to different residual heredity, to variations in gene potency, as in a multiple allelomorphic series or sometimes even to modifying genes when such entities can be clearly demonstrated."

The social aspect of this problem should not be lightly overlooked. Among 181 cases affected, only 72 have married. G. S. admitted that most of those affected, whom he knew, were quite sensitive with regard to the rather disfiguring nail defects. Although he would not admit that it had any relationship to matrimony, the fact remains that a relatively small number have married, who otherwise seem to be healthy individuals. This is especially unfortunate in females. Those marrying may expect that approximately one-half of their offspring will show some abnormality. On the other hand, normal parents, though belonging to the family tree, may expect normal children. The nature of the disease does not indicate that beneficial results may be expected from glandular therapy. The social facts involved may eventually eradicate this syndrome, and further illustrates nature's tendency to overcome abnormalities in the human race.

Summary. 1. A case of hereditary onychial dysplasia is reported. The findings in the family tree to which this individual belongs are given.

2. A new theory of the genesis of this syndrome is presented. It is suggested that the defects observed are due to the differential effects of one gene (D), acting during the process of development of the three primary body layers, its action ceasing on full development of the various parts. The gene (D) may not be entirely dominant.

3. The social aspects of the syndrome are discussed.

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THERAPY IN CARBOLIC ACID POISONING.

WITH SPECIAL REFERENCE TO THE USE OF OIL ANTIDOTES.

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For some years one of the most popular forms of suicide has been by the use of products of the carbolic acid group, and especially with the common commercial preparations such as lysol. A survey of the last 100 cases of poisoning admitted to the New Haven Hospital disclosed that phenol and lysol led the list, comprising the offending agents in 26% of the series; bichlorid of mercury and carbon monoxid constituted 25% and 23%, respectively, of the cases in this group. Phenol and lysol were the cause of death in 45% of those cases with fatal outcome.

The low fatal dosage of this poison and its dramatically rapid and toxic action on the heart, bloodvessels and central nervous system leading speedily through cardiovascular collapse and respiratory failure to death, often within an hour, emphasize the vital importance of prompt and effective treatment.

Among the many antidotes that have been recommended and employed (milk, egg albumin, alcohol, glycerin, sodium sulphate, potassium permanganate, syrup of lime) none has gained universal or enthusiastic acceptance, and only a few have survived in medical practice. Although gastric lavage with alcohol or sodium sulphate is probably the commonest current treatment, it is noteworthy that

* Completed during tenure of a National Research Council Fellowship in Medicine, 1934.

Macht,¹⁴ on the basis of experimental and clinical observations, considered alcohol not only ineffectual, but actually harmful, and Sollmann²¹ (p. 644) brands both alcohol and sulphates as "practically useless."

The incessant search for a suitable antidote for carbolic acid poisoning had at one time resulted even in the suggestion that camphor be used, since a mixture of camphor and phenol is comparatively non-irritating locally. But experimental work by Bond and Haag² quickly demonstrated that the two drugs have similar central nervous system actions, and that camphor definitely increases the toxicity of peroral phenol.

Robertson's exsanguination-transfusion procedure¹⁸ was also tried in experimental phenol poisoning in dogs by Haskell and co-workers⁹ in an attempt to improve the therapeutic attack. They found this procedure to be as valueless for phenol as it proved to be in mercuric chlorid poisoning.¹⁰

The question of the value of alcohol in the treatment of acute carbolic acid poisoning deserves special attention. The history of how alcohol came to be employed wrongly is given by Macht¹⁴ and Wilbert.²⁷ Alcohol still enjoys wide use either in dilutions ranging from 10% to 40% or in the form of strong whiskey. There is little unanimity of opinion, however, as to its value. Most of the older textbooks of toxicology recommend its use, and do not even warn against leaving it in the stomach. Sollmann²¹ (p. 644), as stated, though branding alcohol as a useless chemical antidote recommends that a 10% solution might be employed as a lavage, to be followed by warm water. Underhill²⁵ (p. 187) suggests a similar procedure. The theory underlying the use of alcohol seems to be that, since it is an excellent solvent for phenol and can be shown to be effective in the local treatment of phenol skin burns, therefore it must necessarily, when given for peroral carbolic acid poisoning, dissolve the phenol, delay its absorption, and prevent caustic lesions of the gastric wall. It has been shown, however, by Clarke and Brown⁴ that local gastric lesions from carbolic acid are as severe when phenol is given in alcohol or glycerin solutions, as when given in watery solutions. These same authors, in addition, found no evidence for a chemical antagonism between alcohol and phenol, and could not convince themselves from both clinical and experimental investigations that alcohol had any superiority over water as a lavage medium. Indeed alcohol and phenol placed in the stomach gave results no different from those with phenol alone. Macht¹⁴ found that gastric lavage with alcohol following experimental phenol poisoning in dogs and cats tended to increase the rapidity of onset and severity of symptoms, and to hasten death. It must be remembered that alcohol is one of the few drugs that is absorbed from the stomach, and during absorption carries the dissolved phenol along with it. Indeed, the gastric irritation and vasodilatation resulting from alcohol may tend to hasten absorption. That this is so might be inferred from the work of Dunn and Perley,⁵ who noted that when phenol was administered in alcohol by stomach tube to rabbits the free blood phenol rose more rapidly than when phenol was given alone, although the final levels reached before death in the two groups were essentially the same. These same authors note an apparent increase in toxicity when alcohol is given with phenol and call attention to the possibility of superimposed alcoholic poisoning.

The conclusion to be drawn from the more carefully performed experimental work and critically interpreted clinical data is that alcohol probably does little if any good in phenol poisoning, and may actually do harm.

Notwithstanding the arguments for and against the use of alcohol or any other therapeutic measure, it is evident to anyone who surveys the literature on phenol poisoning, or attempts to treat these unfortunate cases, that a satisfactory antidotal agent is still lacking.

Absorption, Fate and Excretion of Phenol. An understanding of the absorption, fate and excretion of phenol is essential before rational and effective therapy can be instituted. Phenol, C_6H_5OH , carbolic acid, has the characteristic properties of the series of antiseptic benzol derivatives so widely used in industry and medicine. It is slightly soluble in water (1 to 15) but readily miscible in all proportions with alcohol, glycerin and fats. It is not a true acid, and injures tissue by virtue of its being a general protoplasmic poison. It is readily absorbed from all surfaces of the body. The gastro-intestinal absorption, although rapid at first, is slowed after a short interval and may even stop completely, due to local circulatory changes (Sollmann and co-workers²³). This is an important consideration in the treatment of peroral poisoning, for one may still recover phenol from the stomach for some interval after ingestion. In experienced hands, the use of the wash-out tube is usually indicated, and although discretion is necessary in deciding when to employ it, the danger of perforation of the injured esophageal or gastric wall is probably overemphasized. The phenol after absorption is distributed throughout the tissues of the body. It rapidly leaves the blood, and the higher concentrations are found in the liver, brain and kidneys. From 25% to 67% is completely burned by the body, and conjugation of much of the remainder represents an important protective mechanism of the animal organism. A small part of the carbolic acid is oxidized in the body to hydroquinone and pyrocatechin. That which is not burned is excreted in the urine, a trace being eliminated in the sweat. The urinary phenol is both conjugated, especially as ethereal sulphates and phenolic glycuronates, and unconjugated, the former increasing in amount as the total phenol content of the urine increases. The site of conjugation of phenol in the body has been the subject of considerable investigation. Pelkan and Whipple¹⁵ maintain that the liver is the only organ performing this function, whereas Smith,¹⁹ in a recent work, claims that the kidneys and intestines also participate. The occurrence of phenol-sulphonates in the urine led to the mistaken use of sulphates in the attempt to detoxify carbolic acid in the body. As is occasionally the case with a therapeutic measure whose chief virtue is its novelty, the sulphates were reported to be very useful in treating patients poisoned with phenol. That sulphates are not readily absorbed by the alimentary canal is common knowledge, and even if they were, there is evidence to show that sulphates or inorganic sulphur compounds do not increase conjugation. At any rate, the combination between phenol and sulphates does not occur in the intestinal tract, thus rendering oral sodium sulphate for antidotal purposes a useless gesture. The type of conjugation that does occur in the tissues is very slow, so that even when injected intravenously, sulphates are ineffective (Sollmann and Brown²²). Indeed, as long ago as 1895, Tauber²⁴ noted that oral, subcutaneous or intravenous sodium sulphate did not protect against the just fatal dose of subcutaneous phenol in rabbits. It would appear that any slight value the sulphates may occasionally have in the peroral therapy of phenol poisoning is probably due to the purgative effect

of sulphate salts. The symptoms of acute poisoning, in addition to the local effects at the sites of absorption, are mainly referable to the cardiovascular and nervous systems, and the kidneys, all of which are quickly involved. Cardiovascular collapse may ensue from a direct depressant action on the heart muscle and from dilatation of the bloodvessels, with a consequent marked fall in blood-pressure (Gunn⁸). Faintness, weakness, tremors, and respiratory embarrassment and depression are all attributable to the effects of the drug on the central nervous system. In some animals, characteristic and marked generalized clonic convulsions occur, but these are rarely seen in man. The renal damage may result in oliguria and serious impairment of the water and electrolyte balance of the body. The scanty, smoky urine contains albumin, casts, blood (Wakeman and co-workers²⁶) and paired phenolic products.

The Rationale of Therapy in Carbolic Acid Poisoning. This understanding of the absorption, fate and excretion of phenol should now make it obvious that the immediate and most important efforts should be made to prevent or delay the absorption of the poison from the alimentary tract. No adequate means are as yet available for dealing with phenol once it has been absorbed, and to hasten its excretion by the kidneys would hardly alter the course of acute poisoning for several reasons. By the time the renal elimination of phenol is well under way, the kidneys are already injured, damage has been done to the more vulnerable cardiovascular and nervous systems, and excretable phenolic products have already been largely detoxified by the organism through conjugation.

How may one prevent or delay absorption of carbolic acid after ingestion? Three ways immediately present themselves: (1) The phenol may be removed by the stomach tube and lavage. (2) A selective solvent may be administered whose affinity for phenol exceeds that of the protoplasm of the enteric wall, and absorption would thus be prevented or delayed. This solvent could also serve as an efficient lavage medium. (3) One may hasten the passage of the phenol, preferably after it has been taken up by the solvent, along the intestinal canal. This latter method would apply mainly to that portion of the phenol which had passed the pylorus or escaped stomach lavage; it could be accomplished by a carefully selected cathartic. The ideal solvent should, of course, hold the phenol inert; should not itself be absorbed by the gastro-intestinal tract; should not be broken down by enzyme action; and should be harmless.

In view of so dire a need for an acceptable antidotal solvent, it is natural that great interest should be aroused by Gibbs'⁷ recent proposal. He advises the use of paraffin oil* in phenol poisoning and describes it as a simple, effective, safe and logical agent. The rationale of his treatment seems to be based on the presumption that carbolic acid is more soluble in mineral oil than in water, and

* Synonyms for paraffin oil are: Liquid Petrolatum, U. S. P.; Liquid Paraffin, B. P.; white mineral oil.

theoretically leaves the watery medium of the stomach contents for that of the oil, in which it remains pharmacologically inert. Gibbs' treatment of a poisoned patient would require simply the oral administration of a liberal quantity of paraffin oil, which would theoretically take up the carbolic acid efficiently; and since the oil is entirely non-absorbable, it readily assists its own elimination along with the dissolved poison. It is even suggested that if the above therapy is followed by repeated doses of magnesium sulphate, the use of the wash-out tube may be omitted.

On the basis of Gibbs' claims, paraffin oil would indeed be a splendid antidote, for it is a common and easily available substance, and would fulfill the therapeutic requirements outlined above.

Within a fortnight of the appearance of Gibbs' article, however, this therapeutic measure was attacked by Bowdler,³ whose comments were published in the same journal. This writer, a former phenol manufacturer, had learned from practical experience and personal observation that phenol was not at all readily soluble in liquid petrolatum in the presence of water, and he questioned the soundness of Gibbs' procedure. This refutation appeared simply as an obscure letter in the section devoted to "Correspondence." Gibbs,⁷ in a brief rebuttal, defended his original thesis, but still offered no experimental or clinical evidence for his contentions.

It appears probable that the well known ready solubility of carbolic acid in most fats and oils of vegetable and animal origin gave rise to the mistaken notion, which does not by any means follow, that phenol is also readily and highly soluble in the hydrocarbon series of paraffin oils. To clarify this question we have performed solubility tests.

Experiments on Petrolatum Liquidum. The *in vitro* solubility of both carbolic acid crystals and phenol liquefactum in petrolatum liquidum was tested; various dilutions were prepared at both room and body temperatures. Far from being readily and highly soluble, both of these products were very slowly and poorly soluble in mineral oil. Neither by vigorous and repeated shaking, by elevating the temperature, nor by prolonging the contact for days could the solubility be increased above 1 part in about 50. These results agree with those of Pilcher,¹⁷ but are at variance with the statement of Solis-Cohen,²⁰ (p. 746) that phenol is "very soluble" in liquid petrolatum. The solubility of phenol in mineral oil in the presence of water was also tested. It was found that when phenol in dilutions of 1 in 5 to 1 in 30 in water were added to paraffin oil, the latter took up much less of the phenol than formerly. Since phenol is three times as soluble in water as in mineral oil, and definitely prefers protein to water, it is difficult to understand why one should expect phenol to be soluble in mineral oil in the presence of the watery medium of the gastric contents. If a conclusion were to be drawn from these *in vitro* solubility experiments, it would be that petrolatum liquidum is not the long-sought antidote for carbolic acid

poisoning, and that its employment might be dangerous in entailing loss of valuable time needed for more effective therapy. It is interesting in this connection to note that Boenninghaus¹ has reported the destruction of the tympanic membrane and corrosion of the external meatus from the use of liquefied phenol in liquid petrolatum as ear drops for earache.

Because of the importance of confirming definitely the conclusions suggested by the above *in vitro* tests, it was thought desirable to submit the question to actual animal experimentation, even though it seemed unlikely that mineral oil might still delay absorption by some other, perhaps mechanical, means. The necessity for such verification was brought home to us more pointedly by the knowledge that the mineral oil therapy of carbolic acid poisoning had permeated into hospital emergency rooms, and had at one time gained a brief trial at the New Haven Hospital. Furthermore, this treatment is recommended in the current edition of a well-recognized textbook of therapeutics (Beckman,²⁸ p. 696).

Procedure. Normal, adult albino rats, weighing from 100 to 300 gm., and maintained in good health on an adequate diet were used in 150 experiments. In addition, some experiments were done on other laboratory animals in order to make certain that the results obtained with rats were applicable also to other species. Food was first withheld for 36 to 48 hours to insure that the stomach would be quite free from food, water being supplied *ad libitum*. Freshly prepared phenol liquefactum and the various antidotal agents were administered by stomach tube. All animals succumbing in the experiments were autopsied to rule out traumatic death from stomach tube injury, and to recover for study the gastric contents of carbolic acid and antidote.

It was first necessary to establish the minimal lethal dose of phenol for our colony of rats, since the figures given in the literature were found to be excessively high. Hefter¹¹ (p. 912), for example, gives the lethal dose for the rat, determined by Duplay and Cazin, as 0.66 gm. per kg. It was determined on the basis of 20 rats that 0.3 gm. of phenol liquefactum* per kg. of rat could be relied on to prove fatal in 85% of the cases, and we have employed this as the minimal lethal dose (M.L.D.). When this dose was reduced to 0.2 gm. per kg., the fatality was less than 50%.

The sequence of development of symptoms after phenol is given to the rat is constant and rapid. For from $\frac{1}{2}$ to 4 minutes (average of 2) the animal presents no signs. Then respiratory distress appears as the first evidence of intoxication, followed quickly by intermittent muscular twitches of the trunk and extremities. Within another minute or two, the rat loses the ability to maintain normal posture. The animal falls on its side and exhibits severe and extremely rapid clonic convulsions resembling running movements. Since phenol in these doses is an efficient local anes-

* One cubic centimeter of phenol liquefactum weighs approximately 1 gm. Phenol liquefactum is about 90% carbolic acid by weight.

thetic, the animals give no evidence of pain. The convulsions persist until death approaches, becoming less violent toward the end, due probably to the intervention of exhaustion and asphyxia. Respiratory failure ends the picture. Death occurs in from 2 to 50 minutes after phenol (average of 27) but is occasionally delayed for several hours. If recovery is to occur, an early sign is the ability of the rat to regain its feet. Recovery, as far as the appearance and activity of the animal are concerned, is complete, and no late deaths have been noted.

Due to the rapidity of onset of severe symptoms, the antidote had to be given almost directly after the phenol. If one waited for more than 2 or 3 minutes, *i. e.*, until the animal exhibited marked central nervous system signs, then the passage of the stomach tube to administer the antidote was in itself likely to precipitate or hasten death, due to the unavoidable slight respiratory embarrassment occasioned by this procedure. Consequently, it seemed desirable in testing the value of so questionable a therapeutic agent as paraffin oil to administer the oil even before the phenol. If this alleged antidote should fail to protect against the poison under these especially favorable circumstances, then it would indeed be useless to employ it clinically.

TABLE 1.—INEFFECTIVENESS OF MINERAL OIL AS AN ANTIDOTE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of antidote phenol	Intensity of symptoms.	Average time after phenol administration.				Survivors.	
						Appearance of symptoms.	Death.	Recovery.		Number.	Percentage.
						min.	min.	hrs.	min.		
20 . .	M.L.D.	None	Severe	2.0	27	3	..	3	15
20 . .	M.L.D.	Mineral	Before	40	Severe	1.3	33	3	20	4	20
5 . .	2 M.L.D.	Mineral	Before	40	Severe	0.5	12	0	0

Mineral oil was administered to rats by stomach tube in a volume equal to forty times that of the phenol liquefactum given. This volume ratio of oil to phenol closely approximated the solubility ratio without unduly encroaching on the limit of capacity of the rat's stomach. The animals were observed for at least 5 minutes to make certain that nothing in connection with the giving of the oil had affected them adversely; and phenol liquefactum was then given. Twenty rats were given the M.L.D. of phenol following mineral oil, and 5 rats were given twice the M.L.D. Of the former group, 4 lived, 20% survival. Of the latter group, all succumbed. These results are given in Table 1. It is readily seen that mineral

oil, even when given *prior* to phenol does not protect against the poison. The percentage survival was raised from 15%, when no antidote at all was given, only to 20%, a negligible difference. The giving of mineral oil prior to phenol did not delay the onset of symptoms of poisoning or mitigate their severity. Indeed, if it did anything, it increased slightly the speed with which symptoms developed (average of 1.3 minutes after phenol as compared with 2 minutes for the controls). Nor did the paraffin oil manifest any appreciable tendency to delay the time of death, the rats dying in an average of 33 minutes after phenol as compared with 27 minutes for the controls. Likewise, the time needed for recovery was not shortened. An animal was regarded as having recovered when it had regained its feet and ceased to manifest tremors. An examination of the stomachs after death revealed the unabsorbed, undissolved phenol clearly layered underneath the much larger bulk of supernatant liquid petrolatum. Qualitative tests of the oil showed that only a slight trace of carbolic acid had been dissolved.

Since in these experiments only the minimal fatal dose of carbolic acid had been used, and the paraffin oil had been given *beforehand*, one is justified in concluding that not only is mineral oil an ineffectual antidote, but that it fails even to exercise a mechanical hindrance to the rapid absorption of phenol.

In addition to the aforementioned experiments on rats, we tested the antidotal value of liquid petrolatum in 2 each of rabbits, cats, dogs and guinea pigs. In no instance did it protect in the slightest against the fatal dose of carbolic acid. Although these experiments on other species were limited, we believe the general conclusions from the more extensive rat experiments are applicable to other animals, because the principles underlying the absorption, fate and excretion of phenol are essentially similar, and the factors pertaining to absorption in particular are largely mechanical (time, amount, dilution, solubility, absorbing surface, etc.). In this connection it may be mentioned that Sollmann and co-workers²³ found the absorption of phenol to be quantitatively identical in dogs and cats, despite the greater susceptibility of the cat for phenol; and absorption from the stomach and intestines is similarly identical.

Experiments With Olive Oil. Because of these disappointing although predictable and anticipated results with paraffin oil, it was decided to seek a commonly available oil which *would* accomplish what had mistakenly been claimed for liquid petrolatum. The knowledge that phenol is readily miscible with true oils naturally confined the search to those oils of animal and vegetable origin. When none was found that met our requisites we consulted Dr. Wm. E. Anderson of the Department of Physiological Chemistry, who stated that he knew of no true fat that was not readily absorbed by the gastro-intestinal tract. It seems, indeed, from the studies of Langworthy¹³ on 21 animal and 33 vegetable fats, and 3 hydro-

generated oils that their digestibility is uniformly almost complete (approximately 81% to 99%). A mixture of tripalmitin and tristearin (Holt and co-workers¹²) was the only fat that was found with a relatively low digestibility (61.5%). This mixture, however, is not only difficult to obtain, but has a melting point of 50° C., both factors precluding its usefulness. It thus became evident that any common true oil which would act as a solvent for carbolic acid would also in time be digested and absorbed. Recognizing the importance of delaying absorption, and realizing the possibility of using the solvent chiefly as a lavage medium, we decided to use olive oil in the place of mineral oil in experiments similar to those described above. Since phenol death is usually rapid, it was felt that any agent which prevented a lethal concentration of phenol from accumulating in the tissues would allow one to play for just the necessary amount of time that might spell the difference between life and death, in the interim, of course, employing means to remove the unabsorbed poison or hasten its passage from the body.

Olive oil, which has the advantages of being a common, cheap, bland, and not unpleasant household commodity, is a ready solvent for carbolic acid crystals or phenol liquefactum. We tested the *in vitro* solubility of both of these substances in olive oil at room and body temperatures. Phenol liquefactum was very quickly soluble in olive oil at room temperature, in a ratio of 0.9 to 1, and even more soluble at 37° C. Phenol in crystallin form was more slowly soluble and required some shaking, but at body temperature it was almost as soluble as the liquefied form.

Eleven rats were given olive oil, in a volume 40 times that of the M.L.D. of phenol liquefactum, 5 minutes prior to the poison. Ten animals lived, 91% survival, as compared with 20% for the comparable liquid petrolatum group. We then gave twice the M.L.D. in 15 rats but administered olive oil in a volume only 20 times that of the phenol. In this series, 8 animals survived (53%) despite the larger dose of poison and the marked relative reduction in the amount of antidote. In another 10 rats, the M.L.D. of carbolic acid was given first, and then followed in from $\frac{1}{2}$ to 3 minutes by olive oil in a volume 40 times that of the phenol. Of these, only 3 animals survived, a percentage of 30. The results of these experiments with olive oil compared with those of mineral oil appear in Table 2.

These results suggested that there was a direct quantitative relationship between, on the one hand, the amount of poison and its degree and speed of absorption, and, on the other hand, the volume of antidotal solvent and the rapidity and affinity with which it took up the poison. That the time element was of paramount importance was indicated by the fact that when olive oil was given immediately prior to the M.L.D. of phenol, 91% survived; but when it was given immediately after, only 30% survived. It should be

reemphasized that the rat appears peculiarly susceptible to carbolic acid especially in the speed with which violent symptoms (mainly nervous) and death ensue, and therefore an agent which delayed or averted symptoms or death in the rat when double the M.L.D. was given must have some merit. Macht,¹⁴ in commenting on the use of twice the minimal lethal dose of phenol in his experiments, calls this an "enormous dose." It was also noteworthy that olive oil often delayed death, when it occurred, for several hours; and it not only delayed the onset of symptoms, but in nearly every instance greatly reduced their severity. Whereas the animals not given olive oil developed neuromuscular and respiratory signs in 2 minutes on an average, those given olive oil prior to phenol did not show signs for 9 minutes after phenol was given. Death, when it occurred, was greatly delayed, and the time needed for recovery markedly shortened. Even in the group with only 30% survival, death did not occur for 3 hours. An examination of the contents of the stomach showed a much more complete mixture of the phenol and olive oil than was the case with mineral oil.

TABLE 2.—SUPERIORITY OF OLIVE OIL OVER MINERAL OIL AS AN ANTIDOTE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of antidote phenol.	Intensity of symptoms: mod. = moderate.	Average time after phenol administration.			Survivors.	
						Appearance of symptoms.	Death.	Recovery.	Number.	Percentage.
						min.	hrs. min.	hrs. min.		
20	M.L.D.	Mineral	Before	40	Severe	1.3	.. 33	3 20	4	20
11	M.L.D.	Olive	Before	40	Mild*	9.0	5 ..	2 ..	10	91
5	2 M.L.D.	Mineral	Before	40	Severe	0.5	.. 12	0	0
15	2 M.L.D.	Olive	Before	20	Mod. to severe	4.0	1 40	2 20	8	53
10	M.L.D.	Olive	After	40	Mod. to severe	†	3 ..	5 ..	3	30

* One rat had no symptoms.

† Olive oil was given, as a rule, after symptoms appeared.

These encouraging results immediately suggested that the percentage of survivals might be increased by hastening the elimination of the olive oil-phenol solution. Castor oil was selected as the cathartic of choice, since it is an oil in which *in vitro* tests showed phenol liquefactum to be even more soluble than in olive oil, and

a hydrogogic purgative is naturally to be avoided. Castor oil, furthermore, is often used for the emergency treatment of carbolic acid skin burns in establishments manufacturing this chemical. In order to obviate an additional passage of the stomach tube, the castor oil was mixed with the olive oil in the proportion of 1 part of the former to 4 parts of the latter. Twelve rats were given this mixture of oils 5 minutes prior to, and in a volume 20 times that of, 2 M.L.D. of phenol. Nine rats survived, 75%. Despite this very large dose of poison, two rats were completely protected from symptoms. The time for recovery was shortened, and death was delayed. Symptoms were milder, and their onset was delayed. These results are presented in Table 3, which compares them with those obtained on rats receiving olive oil. One sees that the percentage survival is raised to over 40% by adding castor oil to the olive oil, thus aiding the elimination of the oil-phenol solution, and preventing the digestion and absorption of the antidote. Since phenol is freely miscible with castor oil, it might occur to one to use this oil alone; but a few preliminary experiments revealed, as anticipated, an appreciable fall in the percentage of survivals as compared with the olive oil-castor oil combination. It is probable that the inflammatory reaction incited by such necessarily large doses of castor oil served both to promote shock and to facilitate absorption of the poison by local vasodilatation. Death, however, when pure castor oil was given after phenol, was delayed many hours, and the symptoms were mild and late in appearing.

TABLE 3.—CASTOR AND OLIVE OIL MIXTURE AS AN ANTIDOTE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of antidote phenol.	Intensity of symptoms: mod. = moderate.	Average time after phenol administration.			Survivors.	
						Appearance of symptoms.	Death.	Recovery.	Number.	Percentage.
						min.	hrs. min.	hrs. min.		
15	2 M.L.D.	Olive	Before	20	Mod. to severe	4.0	1 40	2 20	8	53
12	2 M.L.D.	Olive and castor	Before	20	Mild to mod.*	6.0*	2 50	1 55	9	75

* Two rats showed no symptoms.

The next logical step was to use olive oil simply as a lavage medium. In 10 rats, therefore, the M.L.D. of phenol liquefactum was given, followed in $\frac{1}{2}$ to 2 minutes by 40 times the volume of

olive oil, and the stomach pumped out immediately. All 10 rats lived, 100% survival. In 10 other rats, 2 M.L.D. were given and followed by only 20 volumes of olive oil, the latter then being pumped back. Eight of these rats lived, 80% survival. The pumping was done within 30 seconds, as a rule, after the olive oil was given, because a longer wait necessitated a second passage of the stomach tube, and this was almost certain to coincide with or precipitate the onset of severe symptoms, and aggravate the latter through respiratory embarrassment. In spite of the short interval of time allowed for the olive oil to dissolve the phenol, sufficient of the latter was removed to give the results recorded in Table 4, which contrasts these with comparable experiments in which pumping was not attempted. These figures again illustrate the importance of removal of the poison-antidote combination, in this instance by pumping the stomach. Examination of the stomach contents again showed considerable phenol taken up by the oil. Here, also, when death occurred, it was delayed, often for 2 or 3 hours. Symptoms were milder, even though their onset preceded the administration of the antidote.

TABLE 4.—EFFECTIVENESS OF OLIVE OIL LAVAGE IN PHENOL POISONING IN RATS.

No. of rats.	Dose of phenol, M.L.D. = 0.3 gm. per kg.	Oil antidote.	Time of administration of antidote, before or after phenol.	Volume ratio of antidote phenol.	Gastric lavage.	Intensity of symptoms: mod. = moderate.	Average time after phenol administration.		Survivors.	
							Death.	Recovery.	Number.	Percentage.
10 . .	M.L.D.	Olive	After	40	No	Mod. to severe	hrs. min. 3 ..	hrs. min. 5 ..	3	30
10 . .	M.L.D.	Olive	After	40	Yes	Mild to mod.	2 ..	10	100
10 . .	2 M.L.D.	Olive	After	20	Yes	Mod. to severe	2 30	4 ..	8	80

In an attempt to follow through the inferences of these results and to simulate the clinical treatment of phenol poisoning, another group of 10 rats was given 2 M.L.D. of the acid, followed by olive oil and stomach lavage; but in these rats an additional dose of olive oil was given after the pumping. Although this is logical therapy, namely, to allow some fresh antidotal solvent to remain in the stomach after lavage to take care of the poison not withdrawn or that which has passed beyond the pylorus, the percentage survival was not raised above the 80% obtained in experiments with com-

parable dosage and procedure except for omitting the final instillation of olive oil. We believe that this is due to the excessive asphyxia resulting from the additional time needed for changing syringes and injecting the last dose of olive oil. By the time this step is reached in the treatment, severe nervous symptoms are rapidly developing and the respiratory embarrassment at this critical time offsets any advantage of this procedure in the rat.

Discussion. From these experiments there is little doubt that mineral oil has no place in the physician's limited armamentarium against acute carbolic acid poisoning. Phenol and related substances are very commonly used chemicals, and still cause a large proportion of poisoning deaths. The treatment at present is admittedly so limited and ineffectual that when a new therapy is published, often with uncritical and exuberant claims, it is likely to gain widespread and unwarranted use. Years sometimes pass before the disappointing results cause it to be discarded. For this reason it was considered desirable to submit the question of the antidotal value of mineral oil to animal experimentation, and to raise a note of warning concerning its use in human poisoning cases. The experiments with olive oil grew out of the failure of petrolatum liquidum to achieve the results which might reasonably be expected of rational treatment. The survival figures for olive oil cited above seem definitely encouraging. We have had no opportunity as yet to apply the implications of this work to human cases, and, therefore, can offer no direct evidence on this point. While we realize all the caution and qualifications necessary for the transference of the conclusions drawn from animal investigation to man, we still feel that since the treatment of phenol poisoning is so limited and unsatisfactory, the trial of olive oil is justifiable. As emphasized previously, in carbolic acid poisoning, "anything which helps a little may help a lot." Olive oil could be administered promptly in as large a quantity as possible, preferably by having the patient drink it if he is able. Then, in skilled hands, the stomach tube can usually be quickly passed with safety and lavage performed with generous quantities of olive oil. Before removing the stomach tube fresh oil could be instilled and allowed to remain.

It is not our purpose to undertake here a complete discussion of the management of the phenol-poisoned patient, but only to emphasize the importance and nature of the immediate emergency therapy. Symptomatic and supportive measures are employed as the particular needs of the case dictate. The physiologic principles of treatment outlined recently by Peters and co-workers¹⁶ for acute mercury poisoning apply equally well to the carbolic acid case, since there is analogous gastro-intestinal, renal and vascular injury with consequent diminution of serum proteins, and disturbance of the fluid and salt stores of the body. Particular attention should be paid to the administration of liberal parenteral fluids and electrolytes of

suitable composition and, perhaps, to the provision of blood by transfusion. Details of this management may best be gleaned directly from the reference cited.

We are not prepared to suggest the use of a cathartic because of the salt and water disturbances it may possibly entail and the additional gastro-intestinal injury; but if one is given, the choice should fall perhaps on castor oil, which in itself is an even better solvent for carbolic acid than is olive oil. Poisoning by lysol and other cresol derivatives has, in general, the same therapeutic implications as those described for phenol.

Summary. 1. *In vitro* and *in vivo* experiments with petrolatum liquidum did not substantiate the claims made for it as a therapeutic antidotal agent in the treatment of acute carbolic acid poisoning.

2. Similar experiments with olive oil gave promising results.

3. The principles underlying the emergency treatment of phenol poisoning were outlined, and the possible use of olive oil in human cases discussed.

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(Titles have been omitted for sake of brevity.)

THE RECOGNITION OF SOME FORMS OF INTRACRANIAL LESIONS.*

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THE ultimate object of a Roentgen ray examination is not merely to determine the presence of lesions but also to diagnose the nature of the pathologic process. It is, of course, impossible to attain this objective in more than a small percentage of the total number of cases examined, but it is not infrequently possible, in cases suffering from intracranial disease, to be able to state the location of a lesion, which is of tremendous importance even though its nature may remain obscure. It is difficult to state accurately what percentage of cases suffering from intracranial disorders will give sufficient evidence in the Roentgen ray film to permit the recognition of a lesion, or how early such evidence will become visible, because it is comparatively rare for a patient to present himself for examination before the symptomatology becomes rather well established. Unfortunately, both the patient and his physician are reluctant to admit the possibility of intracranial trouble before the condition has progressed to such an extent that there remains but little doubt. Of the proved cases of intracranial disease that we see, which usually present strongly suggestive symptoms, about 70% will give evidence in the films to indicate the presence of disease, while in about 30% it will be possible to arrive at a fairly accurate localization of the process, and not infrequently state the nature of the lesion.

The general signs of intracranial disease are those of pressure, such as: atrophy of the sella turcica, increase in number and depth of the convolutional impressions together with a lack of clarity of their outlines, separation of the sutures, and general halisteresis of the skull bones. The localizing signs are 5 in number: calcification, bone proliferation, bone absorption, localized areas of hypervascularity, and last but not least, displacement of the pineal shadow. In the presence of any one of the localizing signs, a diagnosis may be possible, and with more than one present the lesion can usually be localized and often identified. It is of considerable importance, before beginning a study of roentgenograms of the skull, to be in possession of a history of the case, and if possible, the clinical findings. It might also be added that it is futile to attempt to pass opinions on films of the skull which are not of excellent technical quality and stereoscopic.

The first group of lesions to be considered is that composed of

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the so-called bloodvessel tumors, which constitute only about 2% of all intracranial tumors. These are usually divided into the vascular malformations and true tumors. The malformations may be again divided into the venous angiomas and the arteriovenous or aneurysmal angiomas. These malformations are not true tumors, for as pointed out by Cushing and Bailey, glial tissue can be demonstrated between the vessels comprising the lesion, and as they are essentially congenital in type, they are most frequently discovered in young people. The venous malformations may be found in several forms, but for our purpose they can be grouped under the one heading of angioma venosum. These lesions usually are deeply seated in the posterior half of the cerebrum, although they may begin on the surface of the cortex. The symptomatology is usually slight. Perhaps the most common symptom is Jacksonian attacks. At other times they may be discovered quite accidentally. In about 50% of these lesions, sufficient calcification will be present in the walls of the vessels to make them visible in the roentgenogram, and their recognition depends upon the appearance of this calcification, which is usually in parallel lines which often take on a convoluted form. With a venous lesion there is usually no increase in the depth of the vascular channels on the inner table of the skull and there is no evidence of increased intracranial pressure. In Figures 1 and 2 we have an example of such a lesion which was accidentally discovered in an examination of the sinuses. This case emphasizes the advisability of not confining such an examination to small blocked out areas of the sinuses themselves.

The arteriovenous angiomas also show calcification in about 50% of the cases, and like the angioma venosum they are found almost exclusively in the cerebrum, but unlike the venous angioma they are usually accompanied by a marked increase in the size of one or more vascular channels, and not infrequently give rise to some increase of intracranial pressure. These bloodvessel anomalies may, as previously stated, originate on the cortex and burrow deeply in a somewhat conical shape to finally produce a hemorrhage into the ventricular system. Figure 3 is a good example of an arteriovenous angioma in which can easily be seen the large vessel channels and also, upon close examination, parallel streaks of calcification can be recognized. It might not be amiss to mention the fact that in the presence of an arteriovenous angioma not infrequently a bruit may be heard on careful auscultation of the skull—a procedure all too often neglected. It is of considerable importance to be able to recognize these bloodvessel malformations because their treatment is not surgical, as a rule, for the reason that the surgical removal of such a vascular anomaly usually presents such a formidable problem that its solution is often impossible. Hence, radiotherapy is probably the treatment of choice at present.

Let us now consider the true bloodvessel tumors which are the hemangioblastomas. These occur almost exclusively in the posterior fossa in children, and their site of election is in the posterior portion of the fourth ventricle, so that as may readily be seen, they are usually accompanied by a rapid rise of intracranial pressure and therefore, untreated, their history is short. They are usually composed of true angioblasts and may become cystic. It is rare to find one of these cysts containing sufficient calcium to cast a shadow in the roentgenogram. When seen at operation, they may easily be mistaken for an angiomatous type of meningioma, although it is comparatively uncommon to find a meningioma in a young individual. Occasionally, these hemangioblastomas may be rather widely spread and appear along the spinal cord and in the retina, and when accompanied by cystic kidneys and cysts of other abdominal viscera the condition is known as Lindau's disease. Occasionally when these cysts occur in the retina they may become calcified and so become visible in the roentgenogram (Fig. 4).

Another type of bloodvessel tumor which can often be identified in the Roentgen ray films of the skull is the cavernous hemangioma. It may occur anywhere in the bones of the skull, but when seen in the vault is usually quite characteristic. It forms a fusiform swelling with, as a rule, bone spiculations appearing at right angles to the tables of the skull. It is markedly hypervascular and gives the bone a honeycombed appearance. The lesion is, as a rule, quite definitely circumscribed and appears characteristically as seen in Figure 5. Occasionally it will not be as clearly defined and will merely produce an area of bone which appears to contain many small pinholes, and must therefore be differentiated from the often noted osteoporosis and increased visibility of the diploë, which is most commonly seen in the superior parietal and frontal regions.

While considering bloodvessel tumors we may speak briefly of aneurysms, which in the skull are not of syphilitic origin. It is quite possible that some may be of arteriosclerotic origin, but it also seems highly probable that many of them are the result of congenital abnormalities of the vessels and their walls. The most common arteries to be involved are those about the circle of Willis and the basilar artery. When an aneurysm occurs on either side of the sella it usually produces unilateral erosion of the bones forming the sella turcica and often calcium will be deposited in the vessel walls so that curvilinear streaks of increased density may be seen arching above the pituitary fossa, and in addition it is not uncommon to find erosion of the homolateral optic foramen. Figure 6 is a good example of a carotid aneurysm. Aneurysms of the basilar artery are not easy to recognize as they rarely calcify, so that their recognition is usually dependent upon clinical findings or possibly encephalography.

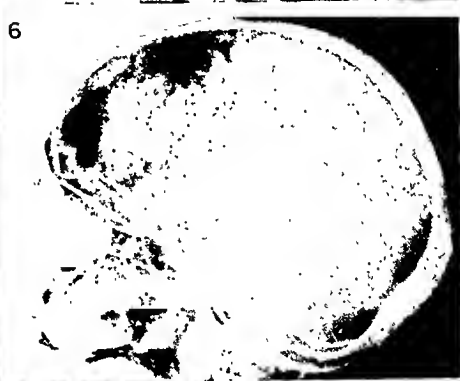
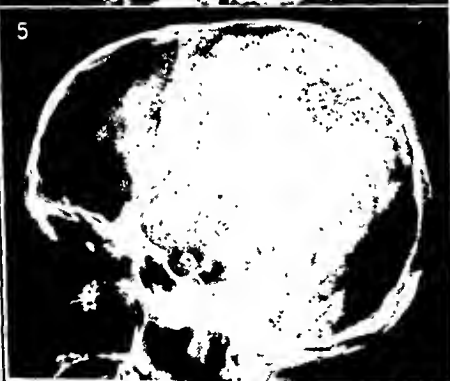
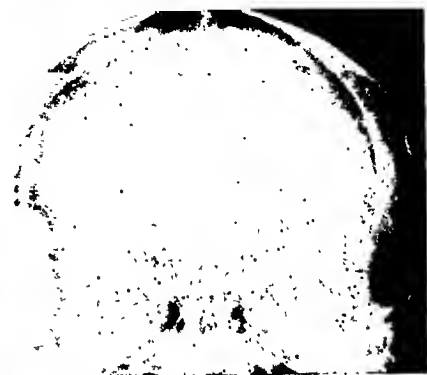
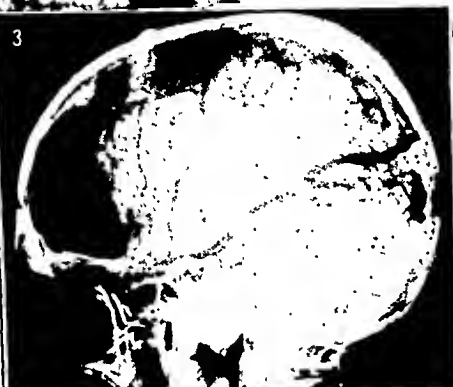


FIG. 1.—A case of angioma venosum. Note the calcification above the tentorium in parieto-occipital region, without signs of increased pressure or hypervascularity.

FIG. 2.—Same case. Note linear parallel streaks of calcification extending obliquely toward midline.

FIG. 3.—Arteriovenous angioma characterized by enlarged vessel channels which are chiefly arterial, and small flecks of calcification in vicinity of the angular gyrus.

FIG. 4.—A case of Lindau's disease. Note circular shadows of calcification in each orbit.

FIG. 5.—Typical case of hemangioma of bone. Occasionally a small anomalous Pacchionian granulation might simulate such a lesion.

FIG. 6.—Aneurysm of internal carotid artery. Note typical curvilinear streaks of calcification and marked destruction of sella turcica.

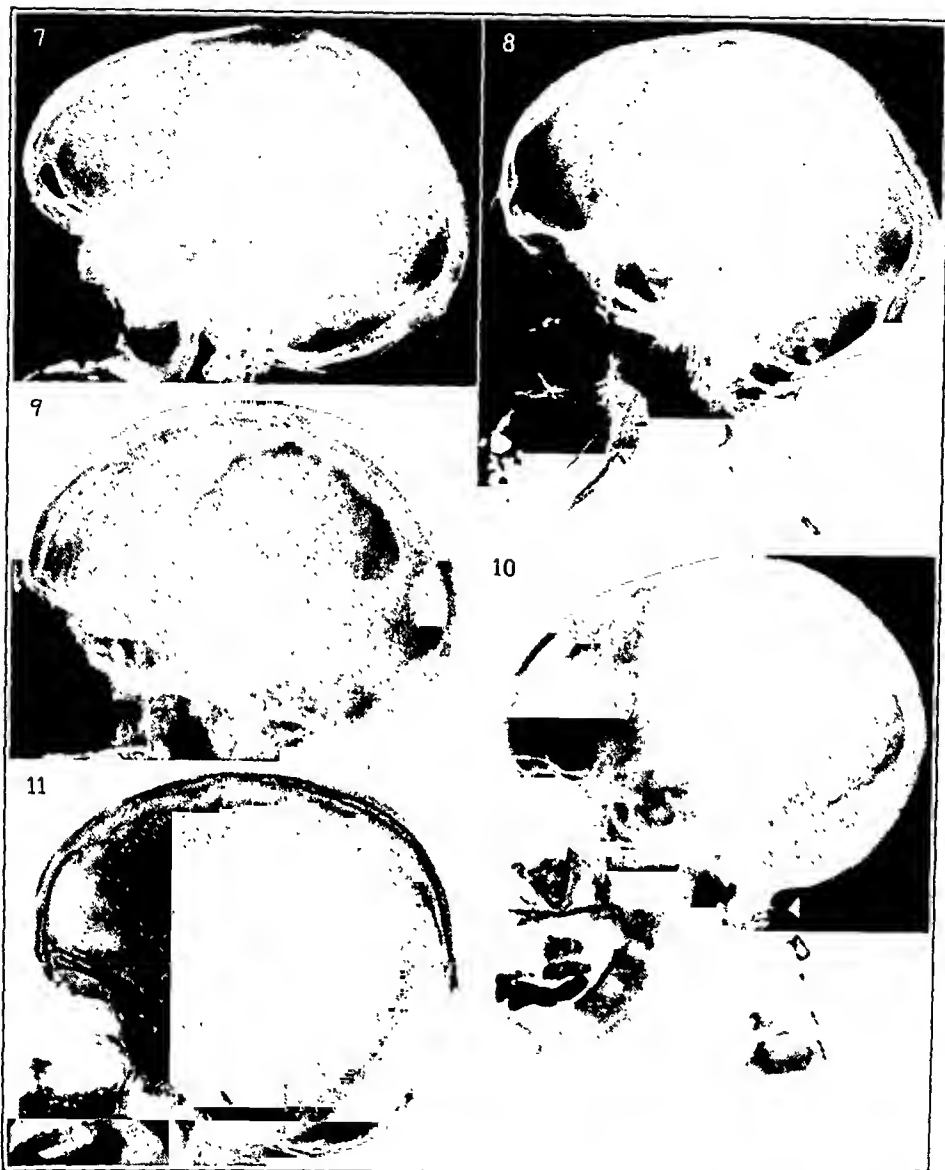


FIG. 7.—Bony overgrowth due to a meningioma of the lesser wing of the sphenoid bone. The extent of the bony change is not a measure of the extent of the tumor.

FIG. 8.—Meningioma producing bony hypertrophy of inner part of sphenoid ridge and extending into the olfactory groove.

FIG. 9.—The large defect in the parietal bone is produced by an epidermoid cyst chiefly involving the diploë. Note the irregular borders of the defect.

FIG. 10.—A typical ballooned sella turcica produced by a chromophobe pituitary adenoma. Note lack of signs of generalized pressure or changes suggesting acromegaly.

FIG. 11.—A good example of a craniopharyngioma. Note the calcification above and the destruction of the sella turcica, together with general signs of elevated intracranial pressure.

The meningiomas, or meningeal fibroblastomas, constitute a group of tumors which are not malignant and do not invade the brain. Their growth is slow and the clinical symptoms may be comparatively slight. These tumors account for about 13% of intracranial new growths and because they are not invasive their complete removal is often possible. It is, therefore, of considerable importance to be able to recognize the presence of a meningioma before it attains such a size that its removal becomes impossible. They probably originate in the meninges and are usually found in certain portions of the skull which constitute their sites of election. About 35% occur over the convexities anterior to the fissure of Rolando. About 25% will be found in the so-called parasagittal location which is along the course of the longitudinal sinus or in the falx. About 12% will be found in the vicinity of the sphenoid ridges and from this location they may extend into the orbits. A slightly smaller percentage will be found involving the petrous ridges. A small percentage will be found originating in the vicinity of the tuberculum sellæ, whereas about 9% occur subtentorially. As a rule, these tumors do not produce much if any increase of intracranial pressure, with the exception of those occurring subtentorially, so that it is not common to find any marked destruction of the sella turcica or other signs of increased pressure. The most characteristic change which can be recognized in the roentgenogram is bone production which is a common finding in the presence of a meningioma. This bone production is apt to be sclerotic when it involves bone of cartilaginous origin, and more spiculated when involving the bones of the vault. It is not uncommon to find sufficient calcium in a meningioma to cast a shadow in the roentgenogram. This shadow is usually homogenous and not dense. If such evidence of calcification is seen in the presence of bone hypertrophy it is almost certainly in one of these tumors. Some of the changes which we have come to recognize as characteristic are shown in Figures 7 and 8. In brief, then, if bony overgrowth is seen in any of the sites of election of the meningiomas, and especially if there is evidence of hypervascularity, there need be no hesitation in making a diagnosis.

Another type of tumor which usually leaves a rather characteristic trade mark is the epidermoid, sometimes known as the cholesteotoma or pearly tumor. This, as the name implies, is of epidermal origin and is most often found in connection with chronic middle ear infections. These tumors may appear in the mastoid antrum but may also be found almost anywhere in the brain or skull. When they occur in the bones of the vault, they usually appear in the diploë and produce an irregular area of osteolysis which is often surrounded by bone of slightly increased density. The margins of the defect are, as a rule, somewhat serpentine in shape and as the tumors are avascular there is no increase in surrounding vascularity.

It is only when the epidermoids involve the bones of the vault or mastoid region that they can be readily recognized in the roentgenogram. The characteristic change produced by such a tumor is well seen in Figure 9. It might be mentioned that such a lesion could be simulated by a leptomeningeal cyst so that such a possibility must be borne in mind when making a differential diagnosis.

Another group of tumors comparatively easy to recognize in the roentgenogram is the pituitary adenoma; but it does not suffice to be able to state merely that a pituitary tumor is present, for in addition we should state whenever possible the type of adenoma we are dealing with. This often can be done if we bear in mind that the chromophobe type of tumor is the most common. It produces the greatest amount of destruction of the sella turcica, and practically no other bony change. The chromophil type of tumor causes less sella destruction but produces the typical changes of acromegaly, or in young people, gigantism. The basophilic adenoma usually produces no change in outline of the sella turcica, because the tumors are often microscopic in size; but there will be a generalized haliteresis which gives a somewhat granular appearance to the vault, simulating slightly the changes commonly associated with hyperparathyroidism. It is also to be noted that as a rule the pituitary adenomas do not give rise to any elevation of intracranial pressure. It also must be borne in mind that sella changes very similar to those produced by pituitary tumors can also occur in the presence of gliomas, but usually the diagnosis can be made if one is in possession of the clinical findings. Not infrequently a tumor will be met containing both chromophobe and chromophil cells; that is, a mixed type, but usually with one or other type of cell predominating. If one should encounter a large, rather well destroyed sella turcica along with changes suggesting acromegaly, the tumor in all probability would be of the mixed type with the chromophilic cells predominating. Figure 10 is of an intrasellar chromophobe adenoma.

After a diagnosis of pituitary adenoma has been made, and unless the eyesight is immediately threatened, I would strongly recommend radiotherapy as the treatment of choice. In our hands it has proved to be startlingly efficient. We have now had the opportunity of following several cases over a period of years and their recovery is evidently permanent.

There is another tumor which occurs in the immediate vicinity of the sella turcica which can often be recognized. This originates from the remains of Rathke's craniopharyngeal pouch. These tumors are essentially congenital and therefore usually a lesion of childhood. Occasionally, however, one will remain dormant and not become evident until adult life. They are slow growing, usually cystic, and prone to calcify. They tend to grow upward and frequently involve the third ventricle so that an increase of intra-

cranial pressure is a common finding. There may or may not be much sella destruction. These tumors frequently are associated with Froehlich's syndrome and are almost always accompanied by visual disturbances. Calcification above the sella turcica with evidences of increased intracranial pressure usually indicates the presence of a craniopharyngioma. The changes produced by such a lesion are shown in Figure 11.

I have purposely omitted mentioning the gliomas because they constitute an extensive subject in themselves, and there is not sufficient time to discuss them in detail. It might be mentioned that it is frequently possible to state that a glioma is present from the changes seen in the roentgenogram, and as about 13% of them calcify, these can, of course, be definitely localized. Occasionally, it is even possible to actually name the type of glioma present.

In this short presentation I trust I have been able to paint for you a "mental picture" of some of the intracranial lesions that can be recognized in the roentgenograms of the skull.

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THE CEREBROSPINAL FLUID DURING AND BETWEEN ATTACKS OF MIGRAINE HEADACHES.*

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MANY of the fundamental factors concerning migraine have never been sufficiently studied. Among these is the relationship of the cerebrospinal fluid pressure and composition to the occurrence of migraine headaches. Riley,¹ in a recent review of the subject of migraine, has emphasized the fact that the data in the literature is based upon the incomplete analysis of fluids from a few cases. There are no reports of the complete findings in an adequate series of cases. For this reason, it is advisable to publish the results of observations of the pressure and composition of the cerebrospinal fluid from 44 patients suffering with migraine. Fifteen of these patients were punctured during an attack.

Bassoe² reviewed some of the spinal fluid observations in the literature and quotes Quinke³ as having obtained pressure readings ranging from 155 to 210 mm. of water during attacks in 3 cases with relief following the lumbar puncture. As reported in the original, 1 of these cases does not appear to be migraine. Kerppola⁴ performed a lumbar puncture in 5 cases of "migraine" and found pressures of 80, 110, 120, 190 and 220 mm. of water respectively. Sicard⁵ and Sicard and Cambessédès⁶ report the findings in a few cases and emphasize the fact that the occurrence of abnormalities in the cerebrospinal fluid is indicative of an organic lesion and is against the diagnosis of "migraine."

Mingazzini⁷ described some of the cerebrospinal fluid characteristics in 48 cases of "essential headache." He avoided using the term migraine and indeed many of his cases could not be classified as such. These "essential headaches," he grouped in two types with separate etiologic factors in each group. One, he feels, is due to cerebral arterial spasm; the other, to a temporary hyperactivity of an angioneurotic choroid plexus. In some cases, especially in the latter type, he felt that the spinal fluid pressure was "augmented" but gives no manometric readings as the pressure was estimated from the rate of flow of fluid from the lumbar needle. Only about

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50% of his cases showed an "augmented" pressure and it was in these cases that the greatest percentage of relief was obtained by withdrawal of lumbar spinal fluid. Other spinal fluid observations he considered to be normal.

Critchley⁸ and Critchley and Ferguson⁹ found a normal fluid under a low pressure in cases punctured during an attack of migraine. The actual pressure readings were: 60, 90, 50 and 75 mm. of water (patient in the lateral recumbent position).

One of us with Pool and Lennox¹⁰ in a study of the effect of ergotamin tartrate upon migrainous and non-migrainous patients reported among other observations the cerebrospinal fluid pressure of 10 migraine patients before and after the administration of ergotamin tartrate. It was pointed out that the cerebrospinal fluid pressure appeared to bear no direct relationship to the occurrence or intensity of the headache in these cases. More complete observations of the cerebrospinal fluid from these cases are included in the present study.

Materials and Methods Used in This Study. All of the observations on patients during headache and most of those in the asymptomatic intervals were made by a member of the Neurological Unit. The remaining cases were collected from the records of the other Services of the Boston City Hospital. The chemical determinations on all the fluids were done by the laboratory of the Neurological Unit.

The patients on whom these observations were made were all subject to recurrent paroxysms of headache for a number of years. In all cases, the headache was associated with nausea and in most cases, with vomiting. Many occurred at the menstrual period. Visual disorders, such as scotomata or blurring of vision, accompanied attacks in many of the cases. Vertigo was a frequent concomitant. A hereditary predisposition was apparent in many but no definite etiology could be ascertained in any of these cases. Cases of obvious neuroses were excluded as well as cases of unproven but suspected intracranial pathology.

Lumbar punctures were performed at the fourth lumbar vertebra while the patient lay in the lateral recumbent position with the craniovertebral axis horizontal. Measurements of pressure were made with an open-end (2 mm. bore) spinal fluid manometer attached directly to the needle. A few minutes elapsed before the pressure was recorded in order that the patient might become quiet and relaxed. After all observations of pressure were made, a sample of the fluid was collected for analysis. Cell counts were made in the ordinary blood-counting chamber, the fluids being lightly stained with Unna's polychrome methylene blue. The total protein was determined by the Ayer, Dailey, and Fremont-Smith modification of the Denis-Ayer method,¹¹ the sugar by the Folin-Wu method as modified by Rothberg and Evans¹² and the chlorids by the Wilson and Ball¹³ modification of the Van Slyke method. The colloidal gold reaction was performed by the Lange method as described by Cockrill.¹⁴

Observations. Our results are presented in Tables 1 and 2. Fifteen observations were made on 15 patients during a typical migraine attack (Table 1). The maximum spinal fluid pressure was 190, the minimum 40, and the average 123 mm. of cerebrospinal fluid. The total proteins were calculated in 13 instances with maximum of 45, minimum of 20 and average of 30 mg. per 100 cc.

In 1 instance the protein was elevated (83 mg. %) due to the presence of contaminating blood, subsequent to trauma at the point of puncture. The sugar content was determined in 4 instances and found to be normal (63, 72, 76 and 80 mg. %) and the chlorid content was also normal in 2 cases (696 and 727 mg. %). Excepting the 2 instances in which blood was present due to trauma at the point of puncture, the appearance, red cell count, white cell count, Pandy test, Ross-Jones test, colloidal gold reaction, Kahn and Wassermann were all normal. In these 2 instances the fluid was that of a typical "bloody tap."¹⁵ The cerebrospinal fluid pressure appeared to bear no direct relationship to the presence of the headache. In 10 cases from 0.25 to 0.5 mg. of ergotamin tartrate was given intravenously after the initial pressure reading was made and before any fluid was removed. Eight of these patients were relieved of headache and 2 were unrelieved following the ergotamin, but without any observable relationship to the alteration in pressure of the cerebrospinal fluid. These cases are reported in detail elsewhere.¹⁰

TABLE 1.—THE CEREBROSPINAL FLUID DURING MIGRAINE HEADACHE.

Case.	Initial pressure, mm. of water.	Cells per c.mm.		Mg. per 100 cc.			See footnotes.
		Red cells.	Lymphocytes.	Protein.	Sugar.	Chlorid (as NaCl).	
CI	40	34	80	727	2, 4, 5
EG	50	31	1, 4, 5
LC	80	1050	4	83	6, 7
HMc	100	0	0	20	1
PG	100	5	0	45
MT	110	28	1
BB	110	12	0	24	63	..	2
EE	110	4	0	31	76	696	3
GF	130	0	0	38	1, 3
VV	145	39	72	..	1, 5
EG	155	0	0	20	1
NJ	165	2	3	25	1
JH	180	292	4	41	7
EM	180	3	2	27	1, 3, 5
AH	190	0	0	20
Averages	123	..	1	30	—	—	—

There were no neutrophils observed. The Ross-Jones and Pandy tests, colloidal gold reaction, and the Wassermann (or Kahn) tests were negative in all fluids.

1. Given 0.25 to 0.5 mg. of I.V. ergotamin tartrate during the puncture with relief of headache.
2. Given 0.25 to 0.5 mg. of I.V. ergotamin tartrate during the puncture without relief of headache.
3. Increased headache followed an increase of the cerebrospinal fluid pressure.
4. Decreased headache followed an increase of the cerebrospinal fluid pressure.
5. Increased headache followed a decrease of cerebrospinal fluid pressure.
6. Decreased headache followed a decrease of cerebrospinal fluid pressure.
7. Bloody tap.

Between the migraine attacks, 34 punctures were performed in 29 patients (Table 2). The cerebrospinal fluid pressure was measured in 28 instances. The results ranged between 190 and 90 mm. with an average of 139 mm. of cerebrospinal fluid. The cell count

in the fluids varied between 11 and 0 lymphocytes with an average of 2 cells per c.mm. Only one fluid had more than 6 cells per c.mm. The protein content was determined in 27 fluids. The results varied between 80 and 11 mg. % with an average of 29 mg. per 100 cc. Only one fluid had a protein content greater than 45 mg. per 100 cc. and in this case the fluid from a subsequent puncture showed a normal protein content. The sugar content was determined in 7 fluids. The results varied from 114 and 52 mg. with an average of 73 mg. per 100 cc. Only one fluid (from a patient with a mild diabetes mellitus) had a sugar content greater than 100 mg. %. The chlorid content was determined in five fluids. The results varied between 769 and 715 with an average of 739 mg. %. The colloidal gold test was normal in all fluids.

TABLE 2.—THE CEREBROSPINAL FLUID DURING MIGRAINE HEADACHE.

Case.	Initial pressure, mm. of water.	Cells per c.mm.		Mg. per 100 cc.			See footnotes.
		Red cells.	Lymphocytes.	Protein.	Sugar.	Chloride (as NaCl).	
ED	90	0	0	23			
JH	90	0	0	37			
JD	95	0	5	31			
ER	100		5				
EM	110	0	5	27	2
JC	110	9	1	16			
ED	120	1	0	34			
WL	120	0	1				
HM	125	0	0	30			
SG	125	70	0	20			
DL	125	..	4	45	93		
MT	125	0	1	34	52	769	
MT	125	2	11	22	74	758	
JG	125	Bloody					
LK	130	0	0	27	2
GS	135	0	0	21			
W	140	0	0	20			
RC	140	630	18	15			2
SB	150	0	0	43	66	..	
MW	150	..	5	33			
MT	160	0	1	20	114	733	1
LC	170	12	2	27			
LP	170	0	0	26	..	721	
NMc	175	0	3	11			
MY	180	..	1	80			
MY	180	45			
GR	180	3	0				
LP	180	0	0	27	..	715	
RC	185	0	2	22			
MG	190	0	6	15			
MD	..	0	3				
LMI	..	0	2				
MC	26	58		
NM	..	0	1	45	55		
Averages	139	..	2	29	73	739	

There were no neutrophils observed. The Ross-Jones and Pandey tests, colloidal gold reaction, and the Wassermann (or Kahn) tests were negative in all fluids.

1. Mild diabetes mellitus with blood sugar of 200 mg. per 100 cc.

2. Bloody tap. Cell count and protein content not included in averages.

Discussion. As is well known, certain forms of headache are associated with and probably dependent upon an increased intracranial (cerebrospinal fluid) pressure. These are the headaches

associated with brain tumors, congestive heart failure, uremia, "meningitis serosa," post-alcoholic "wet brain," and so forth. Such headaches are often increased by an increase in the intracranial pressure and relieved by a decrease in spinal fluid tension. The cases mentioned by Cushing¹⁶ and Thomas¹⁷ and certain of those reported by Mingazzini⁷ fall into this group. Another group of headaches, such as those occasionally following lumbar puncture, are associated with a low cerebrospinal fluid pressure. These are often relieved by increasing the cerebrospinal fluid pressure. Finally there is a large and miscellaneous group of headaches which appear to be independent of the cerebrospinal fluid pressure. It is most likely that the migraine headache falls into this last group.

One of the theories concerning the etiology of migraine implies an increase in the cerebrospinal fluid pressure. This theory postulates a cerebral or meningeal congestion due to toxic or allergic reactions or to intracranial water retention. This congestion is presumed to distend the meninges thus producing headache. If such a congestion occurred it would be expected to produce a measurable increase in intracranial pressure before or during the headache. Our observations with those of Pool *et al.*¹⁰ demonstrate that only rarely is the cerebrospinal fluid pressure elevated in migraine during or between headaches. Our observations also indicate that increasing the cerebrospinal fluid pressure by inhalation of CO₂, jugular compression, coughing and straining, or decreasing it by hyperpnea or the removal of fluid does not consistently alter the intensity of migraine headaches in either direction.

Pickering¹⁸ has observed that the headache following the administration of histamin does not occur until the initial rise of cerebrospinal fluid pressure is disappearing. Similarly, migraine headaches may follow changes in the cerebrospinal fluid pressure which have disappeared before the occurrence of the headache. Other theories suggest that the migraine attack may be due to a localized dilation or spasm of one or more small vessels of the cerebral, pial or dural vascular bed with or without perivascular edema.

Our observations neither add to nor detract from such theories. What observations we have made do suggest the necessity for further observations of the cerebrospinal fluid during the paroxysmal and interparoxysmal periods of "migraine."

Summary. 1. In 15 cases of migraine, the cerebrospinal fluid pressure, measured during a migraine headache, was slightly elevated in 1 case (190 mm. of water), slightly low in 3 cases (40, 50 and 80 mm. of water) and averaged 123 mm. of water.

2. In 29 cases of migraine observed during an asymptomatic interval, the cerebrospinal fluid pressure was slightly elevated in 2 cases (185 and 190 mm. of water), low normal in 3 cases (90, 90 and 95 mm. of water) and averaged 139 mm. of water.

3. In 43 determinations the total protein was normal in all fluids (exclusive of those contaminated by blood) irrespective of the pres-

ence of headache with the exception of 1 case which showed a normal value at a subsequent puncture.

4. In 10 instances, the amount of sugar present in the spinal fluid was within the normal range irrespective of the presence of headache.

5. In 7 fluids the chlorid content was normal.

6. In all cases (44) the Ross-Jones and Pandy tests and colloidal gold reaction were normal except when the spinal fluid was contaminated with blood subsequent to hemorrhage at the point of puncture.

7. The cell count was normal (less than 6 cells per c.mm.) in all but 2 cases which had 6 and 11 cells per c.mm. respectively (bloody fluids excluded).

8. In all of the fluids the Wassermann (or Kahn) test was negative.

Conclusion. We observed no significant abnormality of, nor consistent deviation from the normal cerebrospinal fluid pressure in 44 cases of migraine. The total protein content, cytology and serology of the cerebrospinal fluid were normal. Any significant abnormality of the cerebrospinal fluid renders doubtful a diagnosis of migraine.

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ALLERGY IN MIGRAINE-LIKE HEADACHES.

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THERE is general agreement concerning the use of the arbitrary term, migraine, to designate those cases of recurrent headaches with their allied symptoms of nausea, vomiting and visual disturbance. Because of the almost purely subjective nature of the findings in this disease, it is not difficult to understand the multiplicity of explanations as to the true etiology of migraine, or the even greater number of widely differing therapeutic procedures recommended to bring about relief. That the underlying cause of this common condition is still obscure is evidenced by such wide differences of opinion as recently offered by Riley,¹ Hartung,² Moehlig,³ Vaughan,^{4, 5} Hunt,⁶ Foldes,⁷ and others.

In Riley's exhaustive study and review of the literature of migraine prior to 1932 but slight mention is made of the possible allergic nature of this disease; whereas various other writers have completely disregarded allergenic factors as being of importance. Although an interrelationship between allergy and migraine has been suspected for some time, it was first emphasized by Vaughan⁴ in 1927, and subsequently studied by Rowe,⁸ Balyeat and Rinkel,⁹ Forman,¹⁰ De Gowen,¹¹ Diamond,¹² and other more recent writers. Because of the still prevalent wide differences of opinion in this regard it would seem that it might be of value to present additional evidence in support of allergic factors in the genesis of migraine-like headaches.

The material for this study consists of a series of 127 cases which were seen in the University Hospital during the years 1931 to 1934. In all instances the headaches were localized to the frontal region. In 61.4% head pain was unilateral frontal in location, always occurring upon one or the other side. In 26% the attacks were most frequently bilateral frontal. In the other 12.6% of cases the differentiation between the unilateral or bilateral localization of pain was not recorded.

It should be emphasized that the irregularity in regard to the time interval between headaches characterized this series of cases. The individual attacks varied from instances of almost daily occurrence to a frequency of once in approximately 3 months, or upon

the average of every 18 days. The duration of individual seizures ranged from an hour to that of 7 days, an average of 42 hours elapsing between the initial symptoms and the termination of the postmigrainous manifestations.

Visual disturbances were very frequently, although not invariably, associated. In all instances nausea and vomiting had at some time been present.

Those cases in which other central nervous system disease or involvement of the paranasal sinuses occurred were excluded; errors of refraction were previously corrected. The routine study included a careful history and general physical examination. All patients were routinely tested with 96 food extracts and 25 epidermals as prepared by the method of Coca.¹³ All testing was done by the intradermal method, using 0.03 cc. of a 1 to 1000 dilution for each injection and employing the skin of the back for the test site. In the majority of instances the entire group of injections was done during one afternoon, the readings were made in 30 minutes and again after 18 hours.

In this group of 127 cases there were 95 females (74.8%) and 32 males (25.2%). The average age at the time the patients were first seen was 37 years, the youngest 17 and the oldest 83. The average duration of symptoms had been 20 years.

AGE OF ONSET OF SYMPTOMS. Table 1 shows the age in terms of decades at which time the occurrence of headaches was first noted. Those patients who had the beginning of their symptoms as early as they could remember were included among those in the first decade. It is noteworthy that migraine-like headaches occurred before the age of 16 years in 58% of cases.

TABLE 1.—AGE OF ONSET OF SYMPTOMS IN DECADES WITH PERCENTAGE FOR EACH DECADE.

Years.	Per cent.	Years.	Per cent.
0-10	39.4	31-40	7.1
11-20	33.0	41-50	0.8
21-30	18.9	51-60	0.8

FAMILY HISTORY OF ALLERGY. A familial incidence of allergy was found to be present in 81.6%. A maternal atopic background was evident in 58.4% against a paternal allergic history in 33.6% of cases. Included in these two groups 16.8% of patients revealed a bilateral positive family history. Although allergy did not apparently exist in the familial antecedents of the remaining 6.4%, a history of atopy was found to be present on the offspring of these patients. Table 2 shows the specific incidence of these various allergic states said to have existed in these families. Closer analysis showed that migraine was found in 68% of the families: a history in the mother of 48.8%, and in the father in 20%, whereas in 5.6% of the cases both parents had typical recurrent headaches. Migraine existed in the siblings only in the remaining 4.8%.

TABLE 2.—FAMILIAL INCIDENCE OF ALLERGY.

	Maternal (families).	Paternal (families).	Siblings (families).	Children (families).
Migraine	63	27	30	3
Hay fever*	9	11	10	3
Asthma	8	7	10	3
Eczema	4	4	6	4
Urticaria	2	2	4	5

* Includes both seasonal and perennial hay fever.

PRESENCE OF OTHER ALLERGY. In 43 of this group of 127 cases (34%) an incidence of other allergic manifestations was reported as shown in Table 3.

TABLE 3.—OTHER TYPES OF ALLERGY SHOWN BY 127 CASES OF MIGRAINE.

	Cases.
Hay fever*	22
Urticaria	17
Asthma	4
Gastro-intestinal allergy	4
Sensitization dermatitis	3
Angioneurotic edema	1

* Includes both seasonal and perennial hay fever.

CONTRIBUTORY FACTORS, OTHER THAN FOODS, ASSOCIATED WITH THE PRECIPITATION OF HEADACHES. It had been noticed in the routine histories that patients frequently related their sick headaches with a wide and varied group of extrinsic causes other than foods. A total of 78 cases (61%) gave such a history. It may also be noted that the clinical manifestations of migraine would frequently occur entirely independently of these suspected environmental factors. Table 4 lists these associated agents which were reported by the patients as being influential in the induction of their attacks.

TABLE 4.—CONTRIBUTORY FACTORS SUSPECTED BY PATIENTS AS PRECIPITATING HEADACHES.

Menses	30	Worry	3
Emotional upsets	21	Constipation	3
Excitement	13	Eye strain	3
Fatigue	10	Drafts	2
Exertion	7	Colds	2
Nervousness	6	Dust	2
Warm weather	3	Sunshine	1
Cold weather	3	Noise	1
High humidity	3	Too much sleep	1

FOODS SUSPECTED BY THE PATIENTS AS CAUSING HEADACHES. In 47 cases (37% of the total) it was suspected by the patient that the ingestion of certain specific foods had a direct association with the onset of a migrainous attack. Many patients, entirely by their own volition, had learned to eliminate these articles of their diet. In Table 5 are given the 15 most commonly suspected foods in the order of decreasing incidence.

TABLE 5.—ORDER OF INCIDENCE OF SPECIFIC FOODS SUSPECTED BY PATIENTS.

1. Onion	6. Meat	11. Radish
2. Bean	7. Milk-cream	12. Lettuce
3. Egg	8. Cabbage	13. Asparagus
4. Coffee	9. Peanut	14. Cocoa
5. Tomato	10. Strawberry	15. Apple

FOODS DETECTED BY SKIN TESTING. In Table 6 are listed the foods most commonly found to give positive skin reactions. The minor variations from the lists reported by other writers may be due in part to the dietary habits of people living in this particular geographical area.

TABLE 6.—INCIDENCE OF FOODS GIVING POSITIVE SKIN TESTS.

1. Grains (wheat chiefly)	6. Onion	11. Milk-cream
2. Coffee	7. Peanut	12. Tomato
3. Pea	8. Radish	13. Date
4. Celery	9. Cabbage	14. Spinach
5. Berries	10. Cocoa	15. Carrot

SUMMARY OF RESULTS OF TREATMENT WITH AN ELIMINATION PROGRAM. Each patient was instructed upon a rigid elimination plan in which all skin reacting foods and all foods suspected by the given individual as producing symptoms, regardless of the skin reactions, were entirely removed from the diet. In addition all patients were instructed to keep a dietary diary as described by Vaughan.¹⁴ Upon return visits the results of treatment were evaluated and certain suspicious foods were cautiously added to the diet.

Adequate follow-up information was obtained either by direct questioning upon return visits or otherwise by questionnaire in 77 cases (60.6% of the total group). Of this number it was known that all patients followed instructions completely from periods of time ranging between 6 weeks and 4 years, or an average of 8.5 months. Table 7 lists statistically the results from this type of treatment. By "complete relief" is meant those cases having no recurrence of their migraine headaches during the period in which they were followed. "Excellent relief" includes the group in which headaches were of rare occurrence. "Good relief" indicates those in which the number and severity of attacks were reduced to less than one-half, or in which the seizures were distinctly less severe.

TABLE 7.—RESULTS OF TREATMENT.

	Per cent.
Complete relief	18.2
Excellent relief	20.0
Good	14.3
Fair relief	13.0
Little or no relief	33.7

From the above table, 66.3% were at least partially or completely relieved of their recurrent headaches, in contrast to approximately one-third of the cases receiving no benefit.

It is interesting to note that within this group of 77 cases only 47.7% of the male patients were adequately relieved of their symptoms following their specific elimination program outlined, whereas 72.2% of the females received a satisfactory therapeutic result. Vaughan,⁵ on the other hand, found a correlation between sex incidence and results exactly opposite to this. Of this series of women patients, those in whom the train of migraine symptoms was frequently precipitated by the occurrence of the menstrual cycle received significantly less relief than in that group in which there was no known association with the menses.

Whether attacks of migraine began before or after the age of 16 years apparently made no practical difference in the general response to treatment. Neither did the length of time the patients had suffered from migraine symptoms seem to alter the final results. In like manner the presence or absence of a positive family history of migraine or other allergy appeared to be in no relationship to the expectancy of beneficial returns. Similarly no statistical importance could be derived from the fact that 73.5% of the patients giving a history of suspicious foods were relieved by treatment, whereas 62.8% of the group without such a history were improved.

There seemed to be some evidence to point toward a slightly better prognosis in those patients who gave a history of other associated allergic manifestations than in the group with negative histories in this respect. In the former 24 cases received relief against 7 who were not benefited. In the series with migraine as the only allergic disease present in the family 26 cases were improved with elimination programs against 20 with no change in symptoms.

Conclusions. A group of 127 cases of migraine-like headache, studied and treated from the allergic point of view, has been presented.

The results of treatment in the 60.8% of patients from whom adequate follow-up information was available showed that two-thirds of this number experienced relief of symptoms, partial or complete, following the rigid avoidance of suspected articles of the diet as determined by skin testing and dietary history.

We believe that allergy is an important contributory factor in certain cases of irregularly recurrent migraine-like headache.

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THE RELATIONSHIP BETWEEN URINARY CREATININ AND TOTAL BODY CREATIN, SURFACE AREA, AND BODY WEIGHT.

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THE literature contains many contradictory statements regarding the existence of a relationship between urinary creatinin and body weight, surface area, or other variables. In many of the studies, no account was taken of the influence of the varying quantities of ash, ether extract, and water. Other workers have generally discarded the viscera and skin, and many have not made concomitant determinations of ash, ether extract, and water. Comparatively recent work has shown that the skin contains an appreciable quantity of creatin. In view of these facts, well-controlled experiments have been carried out on rats, in which the comminuted animal, minus the contents of the gastro-intestinal tract, was analyzed for the various constituents.

Body weight was the first variable to be related to creatinin elimination. Folin,¹ in 1904, observed that body weight appeared to be the chief factor determining the amount of creatinin excreted by an individual, and that obese individuals excreted relatively less creatinin per kilo of body weight than lean ones. Then, in 1908, Shaffer² stated that "the amount of Kreatinine-nitrogen per kilo—the kreatinine coefficient—shows a direct parallelism with the mus-

cular development or strength, or 'museular effieieney' of the individual." Muscular development and creatinin elimination were correlated by McClugage, Booth and Evans.³ Patients exhibiting high creatinin coefficients were well-muscled, while those exhibiting low coefficients were either poorly-muscled or excessively obese. These facts were in general agreement with the observations of Tracy and Clark⁴ and also of Hodgson and Lewis⁵ that the creatinin coefficients of athletic women corresponded to those of men. These observations indicate that the fat content of the tissues markedly influences the relationship between body weight or tissue creatin and urinary creatinin.

In infants, Daniels and Hejinian⁶ found that the relation of the creatinin output to the length of the child gave a more nearly accurate estimate of the physical development than is shown by the creatinin-weight relationship. Beard⁷ found that the correlation coefficients between the excretion of creatinin-nitrogen and the body weight, surface area, or height of a large number of students gave little if any evidence for a relationship between these variables.

In 1913, Myers and Fine⁸ found in skinned eviscerated rabbits a constant relation existing between total body creatin and daily creatinin elimination, with the urinary creatinin also following the body weight in every case. In this connection it is of interest that Chanutin and Silvette⁹ have shown that the skin of rats averaged 0.145% creatin.

Mendel and Rose,¹⁰ in their creatin studies on rabbits, recognized the importance of considering the fat, ash, and water. The importance of these factors was further emphasized by Benedict and Osterberg.¹¹ Shaffer¹² called attention to the importance of the water and nitrogen content of tissues used in creatin studies. Relatively few workers have considered the possible influence of these factors upon the interpretation of the creatin-creatinin relationship.

It is apparent from this review of the literature that there is a difference of opinion regarding the relationship between urinary creatinin or creatinin coefficient and various body variables.

Experimental. The rats used in these experiments were mature, healthy animals selected from our colony. Each animal was kept on a diet of 20% dried extracted beef,* 15% lard, 46% cornstarch, 5% cod-liver oil, 5% dried yeast, 4% salt mixture (Osborne and Mendel,¹³ 3% sodium chlorid and 2% agar, until a constant weight had been reached. The metabolism cage used was similar to that of Levine and Smith.

Urine was collected daily for at least 7 days, and as much longer as was necessary to obtain constant results. Weighings were made daily. The rat was killed by a single blow on the back of the neck. Then through a long midline incision the intestines and stomach were removed quickly, opened, and cleared of the contents. The contents alone were discarded. All urine was expressed from the bladder. The entire rat, minus the gastro-

* Valentine Meat Juice Company, Inc., Richmond, Va.

intestinal ballast, was thoroughly ground and mixed. The samples of tissue were placed in covered dishes and weighed immediately. Creatin determinations were made in triplicate while all others were in duplicate. The creatin was estimated by the method of Rose, Helmer, and Chanutin;¹⁴ the urinary creatinin by the method of Folin;¹⁵ and the total nitrogen by the Kjeldahl method. The fat was determined by extracting with ether in a Soxhlet apparatus the dried tissue residue from the total solid determination. The tissue was incinerated over a low flame for ash.

Surface area was estimated by a modified Meeh-Rubner formula.¹⁶

$$S = 12.54 \times W^{0.60}$$

S is the surface area in square centimeters and W is body weight in grams. The formulæ used for the correlation coefficient and its probable error were as follows:

$$r = \frac{\Sigma xy}{\sqrt{\Sigma x^2} \sqrt{\Sigma y^2}}, \text{ probable error} = 0.675 \times \frac{1-r^2}{n}. \text{ In the formulæ,}$$

Σ stands for summation; r , the correlation coefficient; x , the deviation of any item of the first series from the average of that series; y , the deviation of any item of the second series from the average of that series; n , the number of items.

Organic creatin refers to the creatin in the water-, ash-, and fat-free tissue.

Results. The results of the various analyses are summarized in Table 1. The ash, total solids and nitrogen are quite constant, but the fat varies considerably. These results approximate those of Chanutin.¹⁷

The average of the creatinin coefficients is practically identical with that of Chanutin and Kinard.¹⁸ The creatinin coefficients were calculated daily and the average values listed in Table 1.

TABLE 1.—BODY CREATIN AND URINARY CREATININ OF THE RAT.

Number.	Dead weight, gm.	Ash, %.	Total solids, %.	Ether extract, %.	Creatin.		Nitrogen.		Creatinin coefficient.	Average daily creatinin, mg.	Total body creatin, mg.	Surface area, sq. cm.
					Wet, %.	Organic, %.	Wet, %.	Organic, %.				
1 ♀	329	3.50	36.1	12.3	0.311	1.53	16.0	14.4	1004	406
2 ♀	382	3.22	43.4	22.1	0.339	1.88	2.87	16.0	13.6	13.5	1276	444
3 ♀	395	3.41	43.3	21.3	0.300	1.62	2.95	16.2	14.4	14.7	1168	453
4 ♀	317	3.54	40.5	17.0	0.282	1.41	3.19	16.0	14.1	12.1	874	397
5 ♂	469	2.87	42.6	20.4	0.274	1.40	3.15	16.3	13.3	16.2	1263	502
6 ♂	452	3.02	42.8	20.3	0.279	1.43	3.08	15.8	14.4	16.9	1243	491
7 ♂	420	3.22	40.3	16.9	0.315	1.56	3.45	17.1	15.2	16.8	1301	470
8 ♂	382	3.07	43.5	20.8	0.267	1.36	3.14	16.0	12.1	12.6	1010	444
9 ♂	403	3.18	41.4	18.0	0.285	1.40	3.22	15.9	14.0	15.6	1131	459
10 ♂	396	3.46	37.4	13.2	0.308	1.48	3.24	15.6	16.0	16.9	1201	454
11 ♀	329	3.23	47.6	26.6	0.240	1.35	2.81	15.8	13.7	12.3	776	406
12 ♀	269	3.60	40.6	17.2	0.268	1.35	3.06	15.5	15.4	11.2	699	360
13 ♀	248	3.42	42.0	19.4	0.263	1.37	3.15	16.4	14.5	9.6	636	343
14 ♀	272	3.00	41.4	18.6	0.293	1.48	3.07	15.5	13.8	10.2	779	362
Mean	...	3.27	41.6	18.9	0.287	1.47	3.11	16.0	14.3	13.8	1026	428

The correlation coefficients are collected in Table 2. There is a good correlation between the average daily creatinin and total body creatin or total body weight or surface area. Perhaps there is a slight relation between percentage wet creatin and creatinin coefficient.

TABLE 2.—CORRELATION COEFFICIENTS.

Total body creatin	and average daily creatinin	(0.892 \pm 0.010)
Body weight	and average daily creatinin	(0.904 \pm 0.009)
Surface area	and average daily creatinin	(0.906 \pm 0.009)
Wet creatin, %	and average daily creatinin	(0.301 \pm 0.044)
Organic creatin, %	and average daily creatinin	(0.210 \pm 0.068)
Organic body weight	and average daily creatinin	(0.942 \pm 0.005)
Total body creatin	and creatinin coefficient	(0.000 \pm 0.048)
Body weight	and creatinin coefficient	(-0.170 \pm 0.069)
Surface area	and creatinin coefficient	(-0.168 \pm 0.047)
Wet creatin, %	and creatinin coefficient	(0.349 \pm 0.042)
Organic creatin, %	and creatinin coefficient	(0.093 \pm 0.048)

Discussion. Creatinin coefficients are frequently calculated from the average of the daily urinary creatinin and the body weight at the time of death. The value of the coefficient, therefore, depends upon the single weighing of a rather variable factor, body weight. It appears more reasonable to calculate the coefficients daily or to use the average daily weight and average daily creatinin.

It seems that the percentage wet creatin—taking no account of the varying quantities of ash, water, and especially of fat—should bear a less constant relation to the average daily creatinin than does the “organic” creatin. However, this is not the case.

Myers and Fine⁸ found in skinned, eviscerated rabbits that the ratio between total body creatin and daily creatinin was the most reliable means of comparing these substances because the factor of body weight is thereby eliminated from the calculations. In the present study, in which the skin, stomach and intestines were retained, the correlation coefficient between total body creatin and average daily creatinin of the rat is (0.892 \pm 0.010). This coefficient is slightly lower than those obtained in correlating body weight and surface area with the creatinin elimination.

Myers and Fine also stated that animals with a low percentage content of body creatin exhibited a low creatinin coefficient. Their data only partially confirm the statement, for omitting the two extreme values, the correlation coefficient is only (0.521). In the present study in rats, the correlation coefficient between total body creatin and creatinin coefficient is (0.000 \pm 0.048).

In students, Beard⁷ found little if any relationship between creatinin excretion and surface area, and between creatinin nitrogen and body weight. Our data indicate that the average daily creatinin is related to both the body weight and surface area, but the creatinin coefficient is related to neither of these variables. The correlation coefficient between “organic” body weight, *i. e.*, the total ash-, fat-, water-free tissue, and the average daily creatinin is (0.942 \pm 0.005).

Apparently the total body creatin, body weight and surface area are related to the average daily creatinin, but not to the creatinin coefficient.

Summary. A statistical analysis of data obtained in the rat indicates the existence of a definite relationship between the average daily urinary creatinin and to total body creatin or body weight or surface area.

Apparently there is no relationship existing between the creatinin coefficient and total body creatin, body weight or surface area.

The percentage wet creatin of the whole rat possibly bears a slight relation to the average daily creatinin or creatinin coefficient, but the percentage "organic" creatin bears no relation to these variables.

A very high correlation coefficient was obtained between "organic" body weight and the average daily urinary creatinin.

In all the experiments, the whole animal, excepting the contents of the stomach and intestines, was used for analysis.

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FAILURE OF INTRAVENOUS HYDROCHLORIC ACID TO SHORTEN ANESTHESIA.*

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IN view of the widespread interest in the announcement that intravenous injections of N/10 hydrochloric acid promptly terminate anesthesia and because of the great practical value of such a discovery, it was deemed advisable to carry out controlled experiments testing the accuracy of this report.

It seems that Miss Moorman,¹ of Joplin, Mo., having found that intravenous injections of hydrochloric acid terminated anesthesia in animals, told Dr. MacGillvra who, with a Kansas City laboratory, verified the results. The injections were then used successfully in a patient in an emergency. In 7 other instances, anesthesia in patients was terminated by the use of the acid.

MacGillvra² reported that the hydrochloric acid injections had accelerated the recovery of rabbits, guinea pigs, rats, monkeys, and 8 human beings under ether anesthesia and 1 human being under avertin anesthesia. No details were given except in the case of the patient under avertin anesthesia. Ellison and MacGillvra³ later discussed the remarkable recovery of this patient and suggested further probable uses of the hydrochloric acid injections.

Shambaugh and Boggs,¹ however, were unable to accelerate recovery from anesthesia in dogs anesthetized with ether or avertin or nembutal by the intravenous injection of N/10 hydrochloric acid. Neither were they⁵ able to shorten the recovery period of guinea pigs, rabbits, dogs, monkeys and baboons from ether, pentobarbital sodium and tribrom-ethanol narcosis. Control animals were used in these experiments.

In view of these differences it was decided to carry out carefully controlled experiments on dogs and rabbits anesthetized with ether, pentobarbital sodium, and paraldehyde³ to study the effect upon the recovery of the animals following the intravenous injection of N/10 hydrochloric acid.

Methods. Mature, well-nourished dogs and rabbits were used in all experiments. In some cases the animals were subjected to anesthesia several times, but only after a rest of at least 7 days.

* Read before the South Carolina Academy of Science, Columbia, S. C. April 6 1935.

Pentobarbital sodium (nembutal) was given by inhalation, and the paraldehyde was given by stomach tube. Ether was administered evenly to a point where respiratory failure appeared imminent. The N/10 hydro-

TABLE 1.—ETHER.*

Animal.	Weight, kg.	HCl, N/10 cc.	Attempts to stand, minutes.	Stands, minutes.	Walks, minutes.
Dog	17.6	10.0	10.0	11.0	11.5
"	17.7	10.0	10.0	10.5	11.0
"	6.4	1.5	9.0	10.0	10.5
"	7.3	5.5	7.0	10.5	11.5
"	10.0	10.0	9.0	11.5	12.5
"	9.5	8.0	7.5	12.5	19.0
"†	6.0	0.0	5.0	7.0	7.5
"†	7.4	0.0	4.0	5.5	6.0
"†	16.2	0.0	5.0	7.0	8.0
"†	18.2	0.0	5.0	6.0	6.5
"†	10.1	0.0	19.0	21.0	21.0
Rabbit	2.2	1.0	3.0	9.0	9.5
"	2.3	2.0	4.0	8.5	11.0
"	2.8	2.0	9.0	11.5	20.0
"	1.9	2.0	9.0	14.0	15.0
"	2.7	2.0	5.5	18.0	21.0
"	2.7	2.0	5.0	7.5	8.0
"†	2.7	0.0	4.0	4.2	5.5
"†	1.6	0.0	10.0	11.0	11.5
"†	2.4	0.0	2.5	5.2	5.5
"†	1.9	0.0	4.5	6.5	18.0
"†	2.2	0.0	5.5	8.5	9.0
"†	2.4	0.0	6.5	7.0	8.0

* Administered by inhalation.

† Control.

TABLE 2.—NEMBUTAL.*

Animal.	Dosage, gr.	Weight, kg.	HCl, N/10 cc.	Attempts to stand, hours.	Stands, hours.	Walks, hours.
Dog	7.9	17.9	5.0	5.2	5.5	6.0
"	3.7	8.3	2.5	6.5
"	7.9	18.0	10.0	9.0	9.8	10.0
"	7.4	16.7	10.0	6.8	8.0	8.0
"	8.2	18.7	10.0	4.0	4.5	4.5
"	8.1	18.4	10.0	3.6	4.6	4.7
"	10.0
"	6.9	15.6	5.0	5.8	6.1	6.1
"†	7.4	16.8	0.0	...	9.5	9.5
"†	8.2	18.6	0.0	5.8	6.0	6.1
"†	4.8	10.8	0.0	13.0
"†	3.0	6.8	0.0	2.8	3.0	3.2
Rabbit	1.1	1.9	1.0	2.6	2.7	3.2
"	1.4	2.4	2.0	...	3.0	3.0
"	1.5	2.6	1.8	2.2	2.2	2.3
"	1.3	2.2	2.0	1.1	1.7	1.7
"	1.4	2.5	2.0
"	2.0	2.3	2.4	2.4
"†	1.5	2.7	0.0	3.0	3.1	3.3
"†	1.7	2.9	0.0	...	2.5	2.5
"†	1.2	2.1	0.0	...	2.1	2.2
"†	1.1	2.0	0.0	1.2	1.3	1.3

* Intraperitoneal injection.

† Control.

chloric acid was injected slowly into the external saphenous vein of the dog and into an ear vein of the rabbit in amounts varying from 2 to 10 cc.*

TABLE 3.—PARALDEHYDE.*

Animal.	Dosage, gr.	Weight, kg.	HCl, N/10 cc.	Attempts to stand, hours.	Stands, hours.	Walks, hours.
Rabbit	52.5	2.7	2.0	1.0	5.9	6.1
"	46.5	2.4	2.0	4.9	5.9	6.3
"	51.0	2.6	2.0	4.3	6.0	6.1
" †	52.5	2.7	0.0	...	5.0	5.1
" †	48.8	2.5	0.0	3.0	4.1	4.7
" †	48.8	2.5	0.0	5.0	5.5	6.0

* Administered by stomach tube.

† Control.

In nembutal and paraldehyde anesthesia time was measured from the moment the prone animal showed evidences of general relaxation until the animal attempted to stand, stood, walked. In ether anesthesia, time was measured from the moment respiratory failure appeared imminent until the animal attempted to stand, stood, walked.

Groups of animals were anesthetized on the same day in an effort to duplicate all conditions. From the groups, random selection was made of control animals. The control animals were treated exactly like the others except that no hydrochloric acid was administered.

Results. Recovery from nembutal anesthesia or from ether anesthesia in the dog and rabbit was not hastened by the intravenous injection of N/10 hydrochloric acid.

Recovery from paraldehyde anesthesia in the rabbit was not hastened by the intravenous injection of N/10 hydrochloric acid.

Discussion. As in all work of this nature, individual differences in reaction were noted. It is felt, however, that a sufficiently large number of animals was used to justify the conclusions.

Immediately following the injection, the respiratory rate increased, as was expected. However, the recovery period was not shortened, but possibly lengthened.

The experiments were not continued further because no evidence whatsoever was found that the hydrochloric acid hastened the recovery from anesthesia.

Summary. Intravenous injections of N/10 hydrochloric acid do not hasten recovery of dog and rabbit from nembutal, ether or paraldehyde anesthesia. Apparently, such injections tend to lengthen the period of anesthesia.

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* It is not possible to compare the quantities of N/10 HCl used with those of MacGivra or of Ellison and MacGivra for these workers gave no detailed data. They mentioned that a total of 8.6 cc. of acid was injected in one patient but no other figures were given. No data were given of their animal experiments.

MULTIPLE MYELOMA WITH HYPERPROTEINEMIA. CASE REPORT.

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MULTIPLE myeloma is a rare disease comprising about 0.03% of all malignancies.¹ Its rarity and consequent unfamiliarity constitute an obstacle to its recognition and account for the "low index of suspicion" among clinicians regarding it. The clinician, confronted by it, is liable to be taken unaware and may fail even to suspect it as a diagnostic possibility. The diagnosis has too frequently been suggested by the radiologist and even the pathologist. Moreover, the range and variety of its clinical manifestations may be confusing. The disease may involve the skeletal, hemopoietic, respiratory, gastro-intestinal and neuromuscular systems. A multiplicity of symptoms and apparently unrelated findings is thus possible and may produce a complex clinical picture difficult, at times, to correlate and interpret. A knowledge of the fundamental pathologic processes entailed, namely tumor growth of hemopoietic tissue with invasion and destruction of bone and bone marrow, is helpful to an understanding of the symptomatology and clinical evolution of the disease. A detailed description of these, however, is beyond the scope of the present report. An excellent one may be found in the fairly recent and exhaustive review of Geschickter and Copeland.^{1,2}

Of the diverse clinical features of the disease none is pathognomonic; several, as isolated findings, are highly suggestive of myeloma and in combination are strong presumptive evidence of it. The authors referred to above have summarized the more important of these essentially as follows: (1) Multiple involvement of the skeletal trunk in an adult; (2) pathologic fracture, especially of a rib; (3) the excretion of Bence-Jones bodies; (4) characteristic lumbar pain with signs of early paraplegia; (5) an otherwise inexplicable and increasing anemia of the primary type; (6) chronic nephritis with nitrogen retention and normal or low blood pressure. The significance of the last two as clinical leads to the diagnosis of multiple myeloma is perhaps not sufficiently appreciated. If, when they occur, one fails to recognize them as unobtrusive indications of the disease, he is likely to be confused or even misled by what would otherwise be valuable diagnostic clues. If the findings ordinarily associated with multiple myeloma are absent or inconspicuous

the existence of an unexplained anemia, especially if it simulates the primary type or the occurrence of an unusual nephropathy may give the only clue to the real nature of the disease. These findings should always prompt a search for Bence-Jones proteinuria and other evidences of multiple myeloma.

The reasons for reporting the present case are as follows: (1) The diagnosis of multiple myeloma was first suggested by the existence of an apparently atypical "nephritis" and an unusual progressive type of anemia which at first largely overshadowed the more clinically characteristic but less strikingly evident features of the disease. It illustrates these particular aspects of myeloma, emphasizes their importance from a diagnostic standpoint and conveniently epitomizes the atypical blood and renal findings. (2) A more pertinent reason, however, was the occurrence of a markedly increased concentration of the plasma proteins. Several writers, in recent years, have called attention to a remarkable hyperproteinemia associated with multiple myeloma. The condition is especially interesting from the standpoint of pathologic physiology. However in several instances it has been accompanied by and probably causally related to a variety of unusual and even bizarre clinical phenomena. This is quite apparent in the few cases that have been reported thus far. It is considered worth while therefore to review these briefly and to report our own observations in the present case.

Hyperproteinemia. Hyperproteinemia is decidedly uncommon. Its occurrence has been reported in several conditions other than multiple myeloma. Perlzweig, Delrue and Geschickter³ and Johansen⁴ found instances in the literature in which it was associated with an undiagnosed case with enlarged inguinal glands, with neoplasms, especially large kidney tumors and with certain types of infections, notably kala-azar. The most striking cases, however, have been found in association with multiple myeloma. It has been known for a long time that cases of multiple myeloma may exhibit abnormalities of the plasma proteins.⁵ These, in most instances, were attributed to Bence-Jones protein in the serum. However the first case of hyperproteinemia, associated with multiple myeloma was reported by Perlzweig, Delrue and Geschickter.³ Geschickter subsequently observed a second case.² Following their report 15 additional cases have been either reported or referred to in the literature. Bannick and Greene,⁶ Peters and Eisenman⁷ and Shirer, Duncan and Haden⁸ each observed 2 cases. Kumpf,⁹ Jores,¹⁰ Johansen,⁴ Reimann,¹¹ Wintrobe and Buell,⁵ Bonniger¹² and Cantarow¹³ have each reported a case. Reimann¹¹ also cited an unpublished case of Medes. These instances of hyperproteinemia are all that have been reported or referred to in approximately 500 cases of multiple myeloma in the literature. This, however, affords no basis for conclusions regarding its incidence, for there have been only approximately 35 reported cases of multiple myeloma in

which satisfactory quantitative investigation of the plasma proteins has been carried out. These figures emphasize the inadequacy of our data and the impossibility of drawing reliable conclusions from it.

We know, however, that the concentration of the plasma proteins in multiple myeloma is quite variable, for in more than half the cases in which they have been determined they have been found to be within normal limits or diminished. Considering the loss of protein through the kidney (serum-albumin and Bence-Jones protein) and the malnutrition and cachexia that commonly occur in the course of the disease, Chester¹⁴ regards hypoproteinemia as more consistent with multiple myeloma. He is of the opinion that repeated observations over prolonged periods would reveal a relatively higher incidence of hypoproteinemia even in those cases in which the plasma proteins had previously been high. Such a view, however, is not confirmed in the present case. Repeated determinations disclosed a marked and sustained elevation of the plasma proteins. In fact the last determination, made on the day of exitus, was actually higher than the figures previously obtained. Peters and Eisenman⁷ pointed out the lack of correlation between total protein values and the nutritive state in conditions in which globulin is elevated. Hyperproteinemia is entirely compatible with malnutrition, the latter being evidenced by reduction in the albumin concentration. The albumin deficit however may be compensated by excessive increases in globulin.

In the cases thus far reported in which fractional analysis has been carried out the abnormally high concentration of the plasma proteins has been shown to be due either to hyperglobulinemia or actual Bence-Jones proteinemia. Perlzweig, Delrue and Geschickter,³ Johansen,⁴ and Bannick and Greene⁶ found high values for euglobulin and less significant amounts of pseudoglobulin I and II. Reimann's¹¹ case is exceptional in that it showed an excessive concentration of fibrinogen (5.48%). Shirer, Duncan and Haden⁸ and Cantarow¹³ demonstrated extraordinary amounts of Bence-Jones protein in the serum of their patients. An actual decrease in the albumin concentration occurred in every instance in which fractional determinations were reported. Jacobson¹⁵ reported a case in which 7.8% of Bence-Jones protein was found in the blood. In view of the fact that no entirely satisfactory method has been devised for the quantitative estimation of Bence-Jones protein in plasma, his figures have been regarded with skepticism by most subsequent writers and Perlzweig, Delrue, and Geschickter³ considered the bulk of the protein in Jacobson's case to have been euglobulin. However, the reports of Shirer, Duncan and Haden⁸ and Cantarow¹³ tend to support Jacobson's findings. Since the figure for Bence-Jones protein in this particular case represented only part of the total plasma protein the latter undoubtedly was high. In 7 cases, including the present one, Bence-Jones protein was found in the

serum or the urine, while in 5 cases it was not demonstrable in either. Thus hypertroteinemia, in some instances, may be due to an actual Bence-Jones protcinemia. However there still remains a larger group in which evidence of a relationship between the two is doubtful or entirely lacking.

The pathologic physiology of hyperproteinemia and its peculiar association with multiple myeloma are entirely obscure. The fact that it is encountered, at least in its most striking form, in a disease otherwise characterized by the occurrence of abnormal protein (Bence-Jones) is worthy of note and indicates a probable bearing on the question of the origin of the plasma proteins in general. Perlzweig, Delrue and Geschickter³ have suggested, in view of the fact that Bence-Jones protein is immunologically distinct from the normal blood and tissue proteins, that it may behave as a foreign protein capable of inducing a systemic reaction with hyperproteinemia, such as is observed in animal and immunization experiments. This hypothesis seems untenable as the evidence at the present time indicates that, in some cases at least, hyperproteinemia may occur independently of Bence-Jones protein while in others it is actually due to Bence-Jones proteinemia. Against it also is the fact that Bence-Jones protein ordinarily occurs in the serum or the urine without the production of hyperprotcinemia. Reimann¹¹ interpreted his observations as being in harmony with the theory that the bone marrow is a source of blood proteins. Certainly the association of hyperproteinemia and Bence-Jones protein with disease of the bone marrow is suggestive of more than a casual relationship between them. The suggestion, however, is less impressive when one considers that fibrinogen, a hepatic product, is likewise uniformly increased. Again, Peters and Eisenman⁷ have found consistent increases in the serum globulin in association with diseases of the liver, an organ also regarded as a possible source of blood proteins. The meagerness of our information concerning hyperproteinemia does not permit any conclusions as to its cause or significance. The whole subject is vague and requires further elucidation.

Why hyperproteinemia should occur in some cases of multiple myeloma and not in others remains unexplained. Quite as inexplicable is the observation that in some cases it has produced no manifestations by which it might be recognized clinically while in others it has presumably given rise to decidedly unusual and quite variable clinical phenomena. In the cases of Bannick and Greene,⁶ Peters and Eisenman,⁷ Kumpf⁹ and Jores,¹⁰ no mention is made of any unusual findings attributable to hyperproteinemia. In the cases in which Bence-Jones proteinemia was present a precipitate formed in the serum at 56° during inactivation for the Wassermann reaction. Perlzweig, Delrue and Geschickter³ found it practically impossible in their case, to obtain serum for blood calcium determinations due

to failure of the blood clot to retract. This finding led them to an investigation of the plasma proteins and the discovery of a hyperproteinemia. In Reimann's¹¹ case the hyperproteinemia was discovered by an inability to count the erythrocytes in the counting chamber due to excessively rapid rouleaux formation. This aroused the suspicion of an abnormality of the blood proteins, most probably an increase in fibrinogen. Autohemagglutination of the erythrocytes was also observed in attempting to obtain a donor for blood transfusion and, likewise, an extraordinarily rapid sedimentation of the erythrocytes. Bonniger¹² also experienced difficulty in counting the red cells in his patient, but in contrast to Reimann's case, the cause was apparently a coagulation of the blood on contact with Hayem's solution. The cells could be counted in physiologic salt solution. This observer also noted that the blood plasma was viscid and sticky and there was a "tendency of the erythrocytes to agglutinate." It is interesting to note that Hopkins and Savory,¹⁶ 23 years ago, were unable to obtain an erythrocyte count in a patient with multiple myeloma on account of too rapid coagulation of the blood. The significance of this was not appreciated at the time. Johansen⁴ could not obtain specimens of citrated blood for examination because of abnormal coagulation of the blood. Serum had to be expressed from the clot apparently because the latter failed to retract normally. Only by using excessive amounts of citrate was he able to obtain a blood count. He also failed to obtain a sedimentation rate due to spontaneous agglutination of the cells. Wintrobe and Buell⁵ observed spontaneous precipitation of protein which occurred invariably on withdrawal of blood from their patient. The latter presented a very unusual clinical picture in which thrombosis of the retinal veins occurred and circulatory changes in the extremities simulated Raynaud's disease. The present case exhibited the phenomenon of autohemagglutination as noted by Reimann¹¹ and a remarkably accelerated sedimentation velocity of the erythrocytes. Thus it is apparent that hyperproteinemia of the degree sometimes encountered in multiple myeloma may account for a variety of unusual phenomena. It is therefore of some practical importance to the clinician and to the clinical pathologist to recognize the significance of these and their probable explanation on the basis of hyperproteinemia. The latter should always arouse a suspicion of multiple myeloma.

Case Report. L. P. (No. 180322), a 48-year-old Portuguese male cook, was admitted to the San Francisco Hospital, on the Stanford Medical Service, February 9, 1934, complaining of pains in the back and right buttock of 3 months' duration and bleeding from a tooth socket following extraction of a tooth 1 month previously. His family history was negative. Except for an apparently uncomplicated pneumonia in 1930 he had been reasonably strong and healthy until the onset of his present illness. There was no history of important trauma.

Present Illness. In September, 1933, about 5 months before his present entry, he was admitted to the San Francisco Hospital with a facial erysipelas which cleared up uneventfully in 10 days. He remained well until December, 1933, 3 months before entry. At that time he developed dull pain in the right lumbar region and right buttock. The pain was at first intermittent, non-radiating and not definitely associated with any activity. It gradually became more constant and severe, with occasional sharp exacerbations and aggravated by sudden movements. The pain continued for a month, at the end of which time, although he sought no medical attention, he was compelled to quit work on account of it. Early in January, 1934, he developed pains in the left scapular region, which subsided gradually and spontaneously after 2 weeks. On January 4, 1934, he had an upper tooth extracted, following which he bled profusely and subsequently continued to ooze blood even during his stay in the hospital. Two weeks before entry he had a brief episode of chills and fever which cleared up in about 12 hours but left him with a slight unproductive cough. For a month before entry he was in bed on account of pain, increasing weakness, cough and bleeding from the gums. He had lost about 30 pounds during the 3 months preceding his entry to the hospital.

Physical Examination. At the time of entry he was moderately emaciated and appeared obviously ill. His temperature was 98.8°; pulse, 80 to 100, and respirations, 20. The mucous membranes and nails showed marked pallor. The pupils and extraocular muscles were normal. Both fundi showed several small hemorrhages and the left fundus showed a large recent hemorrhage. No appreciable sclerosis of the retinal arteries, plaques or exudate were seen. The disks were normal. The picture was not at all characteristic of hypertensive neuroretinopathy. Examination of the mouth showed moderate pyorrhea and oozing of blood from the margins of several upper and lower teeth, the patient frequently expectorating bloody saliva. No local or generalized adenopathy was found. The chest was characteristically emphysematous and marked dorsal kyphosis was present. The lower rib margins approximated the pelvic brim. The heart was negative; blood pressure, 118/70 to 120/74. The lungs were apparently clear. The abdomen was negative and no viscera were palpable. The rectum, prostate and genitalia were normal. There was marked tenderness to percussion over the fifth and tenth dorsal spines. Neurologic examination was negative except for weakness of the right hand and definitely increased reflexes in the right upper extremity.

Laboratory Findings. Blood. The blood showed a profound anemia with a color index greater than 1 on the first examination and 1 or slightly less on subsequent examinations. The hemoglobin varied from 40% to 27% and the erythrocytes from 1,900,000 to 1,400,000. The leukocyte count was normal except for one examination which showed a reduction to 3600. The smears constantly showed myelocytes and normoblasts and on one occasion myeloblasts were present. The red cells showed marked polychromasia and moderate poikilocytosis. Of the neutrophils, 43% were of the non-segmented type, while only 9% to 20% were segmented. The average diameter of the red cells was 8.1 and the average volume 108 cu. μ on a single examination. The erythrocytes showed a normal resistance to hypotonic saline solutions. The bleeding, clotting time and retractility were normal. A platelet count was not made but these were scarce in the smears.

Urinalysis. The initial examination of the urine showed a moderate cloud of albumin, 2 to 5 red cells per high-powered field and a moderate number of granular and hyalin casts. Of 2 Addis concentration tests, the first was suggestive of a hemorrhagic type of nephritis with definite proteinuria and a relatively large number of red cells and casts in the

sediment; the second showed much less protein and a smaller number of red cells and casts. The concentrating power was somewhat diminished.

TABLE 1.—BLOOD PICTURE.

Date.	Hemoglobin, %.	R. B. C., millions per c.mm.	Color index.	W. B. C.	Polymorphonuclears, %.	PNE., %.	PMB., %.	Myelocytes, %.	Myeloblasts, %.	Lymphocytes, %.	Monocytes, %.	Reticulocytes, %.
2/10/34 . . .	40	1.78	1.18	7150	66	1	..	10.0	..	38	10	
2/13/34 . . .	33	1.70	0.99	8600	53	..	1	6.5	1.5	25	13	5
2/20/34 . . .	39	1.99	1.00	6000	63	1	..	1.0	..	22	13	7
3/ 5/34 . . .	30	1.65	0.96	3600	52	38	10	
3/ 6/34 . . .	27	1.41	0.98									

The Wassermann test was negative. The blood urea was 43 mg. %. The histamin test meal gave normal volumes. The free hydrochloric acid varied from 0 in the fasting contents to 96°, and the total acidity from 25° to 104°.

Roentgen examination showed a compression fracture of the first lumbar vertebra and diffuse osteoporosis of the lower ribs and lumbar vertebrae. Films of the skull, pelvis and extremities were negative.

Diagnosis. Multiple myeloma was first suggested by the peculiar blood picture and evidences of an atypical "nephritis." Although these are by no means constant or pathognomonic features of the disease, their combination should always demand consideration of myeloma. This impression was supported by the persistent and distressing character of the back pain and the finding of Bence-Jones proteinuria. The latter was subsequently repeatedly demonstrable in the urine. The Roentgen ray findings were entirely compatible with diffuse myelomatosis of the spine and ribs. The diagnosis also accounted for the emphysema, kyphosis, the localized tenderness over the spine and the compression fracture of the first lumbar vertebra.

TABLE 2.—BLOOD CHEMICAL FINDINGS.

Date.	Total protein.	Albumin.	Globulin.	Fibrinogen.	Serum Ca.	Diff. Ca.	Inorganic P.
2/20/34 . . .	12.8						
2/23/34 . . .	12.0	1.8	10.2				
2/28/34 . . .	11.41	3.66	8.35	..	12.0	7.7	
3/ 6/34	11.3	..	3.74
3/13/34 . . .	13.5	0.75			

The protein determinations were done by the Kjeldahl method.

Plasma protein determinations were made in conjunction with blood calcium and phosphorus studies. The latter gave normal values but the total plasma proteins were found to be markedly increased. The results of these and later determinations are included in Table 2. The finding of hyperproteinemia was considered strong confirmatory evidence for the diagnosis of myelomatosis.

Course. Except for some decrease in the severity of the pain, probably attributable to Roentgen ray, the patient's course was characterized by progressive weakness and gradual failure. The anemia was not influenced by iron or liver therapy. He died March 13, 1934. Unfortunately, consent for biopsy or necropsy could not be obtained. Although pathologic confirmation is lacking, it was felt the diagnosis rested on reasonably firm clinical grounds.

Comment. In view of the high globulin and fibrinogen content of the plasma, which are generally regarded as influencing the sedimentation velocity of the erythrocytes, a sedimentation test was done. The red cells settled with striking rapidity and clumping of the cells could be observed macroscopically. The cells settled a distance of 43 mm. in less than 15 minutes and so rapidly that it was impossible to obtain clear-cut interval readings. The normal sedimentation rate for the method would have been 10 mm. or less in 1 hour. For the same reason it was thought that the agglutination of a prospective donor's cells in the patient's serum might possibly be accounted for by excessively rapid rouleaux formation, as observed by Reimann¹¹ rather than by true incompatibility. A control was done by matching the patient's cells with his own serum. Agglutination of the red cells occurred in the control. Reimann¹¹ points out that this phenomenon of autohemagglutination or pan-agglutination, does not necessarily indicate incompatibility, and in such instances may occur as a result of rapid rouleaux formation, simulating true iso-agglutination. It can be distinguished from the latter by the fact that true iso-agglutinins may be removed from the serum by absorption and are less influenced by dilution of the serum. The practical importance of this is obvious.

The capricious character of these phenomena is indicated by the fact that despite an increased tendency to agglutination of the erythrocytes no difficulty was experienced in counting the red cells in the present instance. Also, in other cases with comparable increases in globulin and fibrinogen, apparently no unusual phenomena whatever have been observed.^{6,7,9,10}

The patient's serum also gave a positive aldehyde test. This test, originally described by Napier¹⁷ is a useful diagnostic test for late kala-azar and is dependent upon an excess of globulin in the serum. The reaction consists in the formation of a white opacity and jellyfication upon the addition of a few drops of formalin to 0.5 to 1 cc. of serum.

Dr. Garnett Cheney, using a method described by Krogh and Nakazawa,¹⁸ found the osmotic pressure of the plasma to be within normal limits (270 mm. water). This agrees with the observations of others who have made determinations of the osmotic pressure of the plasma in hyperproteinemia.^{3,4,7} This is not surprising when one considers the relative molecular size and osmotic influence of albumin as compared to globulin. The former exerts an osmotic

pressure approximately 4 times that of globulin. In the hyperproteinemias thus far observed there has been uniformly a reduction of albumin but the resulting osmotic deficit has been compensated by the hyperglobulinemia.

The peculiar type of anemia and clinical evidences of renal involvement as observed in our patient deserve some comment. Despite the fact that they have been associated with myeloma by various writers their value as aids to the diagnosis is not as yet generally appreciated. Their occurrence is still more likely to puzzle than to help the clinician. To call attention to them again and to emphasize their importance is perhaps not amiss.

While anemia is frequent in myeloma its character is quite variable. In most instances it is of the secondary type and lacks distinctive features. However there occurs occasionally an anemia of the type found in our case which differs from any of the ordinary anemias, either primary or secondary. This is characterized by a relatively high color index in which respect it resembles a primary anemia. It is progressive in its course and apparently uninfluenced by either liver or iron therapy. There is no association with achlorhydria. The leukocyte count is usually normal, any increase in this being usually explicable on the basis of complicating infection. As the anemia increases immature cells may appear in the circulating blood. The smears may show normoblasts, myelocytes and rarely myeloblasts, indicating a rather marked disturbance of the bone marrow with active regeneration. In this it differs from the aplastic type of anemias. There is a tendency for the mononuclear forms to increase. Such a blood picture is not pathognomonic but is sufficiently characteristic of widespread disease of the bone marrow to suggest the possibility of myeloma, especially in the absence of bone metastases from a demonstrable primary tumor.

In view of the recent interest in hyperparathyroidism it may be noted that this possibility was suggested by the Roentgen findings in the present case. The cases observed by Peters and Eisenman,⁷ Jores¹⁰ and Reimann¹¹ likewise simulated the Roentgen picture of hyperparathyroidism or diffuse osteoporosis. Aside from the fact that the Roentgen ray appearance at times may be indistinguishable the two diseases may present certain clinical resemblances.¹⁹ In both, skeletal changes may be prominent and pathologic fractures may occur. Hypercalcemia has been reported in myeloma.^{8,10,11} Secondary renal changes may occur in both conditions although these should be differentiated without difficulty. In the present instance the Bence-Jones proteinuria, anemia, hyperproteinemia, normal blood calcium and phosphorus and absence of clinical signs of hyperparathyroidism pointed strongly to myeloma. Biopsy, not obtainable in this case, is of course usually decisive.

Renal complications occur in approximately 70% of the cases

of multiple myeloma.² The renal changes may be divided into three groups: (1) Those produced by Bence-Jones proteinuria. This group constitutes the most common and distinctive type of involvement. (2) changes merely incidental and in no way properly attributable to myeloma *per se* or to Bence-Jones proteinuria. Among these are the degenerative vascular lesions which might reasonably be expected in any age group comparable to that of myeloma patients. In this group may be included also true glomerulonephritis and nephrosis, both of which may rarely complicate the disease. (3) pyelonephritis and related urinary tract infections incident to lesions of the spinal cord and consequent bladder paralysis. Amyloidosis may occur as a result of myeloma but tends to have an unusual localization, the kidney involvement being rarely marked.

It is with reference to the first group that the urinary findings in our patient are of interest. The latter were atypical and inexplicable on the basis of any of the usual nephropathies. This fact led to a suspicion of myeloma and the finding of Bence-Jones protein in the urine.

Our ideas regarding the relation of Bence-Jones proteinuria to renal injury have been clarified by the recent investigations of Bell,²⁰ who confirmed the original views of Bohnenkamp.²¹ Bell's work has served to simplify the clinical picture and to establish conclusively the pathologic basis for it. The majority of patients, as observed clinically, have proteinuria and less frequently a variable number and variety of casts in the sediment. The proteinuria may be due to the excretion of Bence-Jones protein or serum-albumin or both. Impaired renal function with retention of non-protein-nitrogen may occur and not infrequently progresses to a terminal uremia. The infrequency of hypertension and its concomitant manifestations in these cases is an important and distinctive feature. Gross hematuria and edema ordinarily do not form a part of the picture. Thus the findings differ significantly from those of a true glomerulonephritis and nephrosis. Bell has demonstrated that the pathologic changes in the kidney consist of tubular atrophy due to obstruction of the tubules by casts of Bence-Jones protein. The injury to the kidney is mechanical and not the result of a direct toxic action exerted by Bence-Jones protein, as some writers have believed.²² Pathologically it represents a variety of tubular contracted kidney but as Fishberg²³ points out, "it is more closely allied to the hydronephrotic contracted kidney than to the hypothetical end stages of chronic nephrosis."

Summary. 1. A case diagnosed clinically as multiple myeloma with hyperproteinemia is reported and the cases in the literature reviewed.

2. Hyperproteinemia is decidedly uncommon and occurs, in its most striking form, in multiple myeloma.

3. In the majority of instances it has been attributable to hyper-

globulinemia without demonstrable relationship to Bence-Jones protein. In 3 cases it was due to extraordinary amounts of Bence-Jones protein in the serum. In the present case, both globulin and fibrinogen were increased in the blood plasma.

4. Hyperproteinemia may produce unusual and variable clinical phenomena, notably: difficulty in counting erythrocytes; autohemagglutination; markedly accelerated sedimentation velocity of the erythrocytes; abnormal coagulability of the blood and spontaneous precipitation of protein in drawn blood. In the presence of Bence-Jones proteinemia precipitation in the serum may occur during inactivation for the Wassermann reaction.

5. The finding of hyperproteinemia or any of its manifestations should suggest multiple myeloma as a diagnostic possibility.

6. The clinical aspects of the blood and kidney changes in the present case are emphasized and their diagnostic importance indicated. These include (a) a severe, progressive, macrocytic anemia with evidences of profound bone-marrow disturbance and active regeneration, unassociated with achlorhydria and refractory to liver and iron therapy; and (b) an atypical nephropathy in which impairment of renal function without hypertension is a distinctive feature.

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PARADOXICAL PLEURAL PRESSURES.

THEIR RELATION TO THE KIENBOECK PHENOMENON.

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THE wider application of induced pneumothorax in the treatment of pulmonary tuberculosis in the past two decades has naturally led to a more specific knowledge of the difficulties that may be encountered and complications that may arise in the course of this method of therapy. A vast and instructive literature on the subject now awaits the interested or perplexed. Nevertheless, with the exception of Saugman and Hansen's¹ and Schill's² reports, very little has been said about the extraordinary condition occasionally observed in artificial pneumothorax and correctly termed "Paradoxical Pleural Pressures."

Paradoxical Pressures in Pneumoperitoneum. Although Zink³ claims to have found normal pleural pressure values with the pneumothorax needle in the abdominal cavity, his observations have not been confirmed by reliable workers either in this country or abroad. It is now well known that only paradoxical pressures, *i. e.*, higher pressure values on inspiration and lower pressure values on expiration, are obtained if the pneumothorax needle enters the abdominal instead of the pleural cavity in the course of an inflation.

Orientation in such cases is usually not difficult, because, up to a certain point, the paradoxical pressures remain unaltered in spite of the inflation of a large amount of air. This is due to the fact that the inflated air readily escapes into the general peritoneal cavity. Moreover, the patient may complain of pain in the epigastrium during or immediately after inflation, and classic Roentgen findings of pneumoperitoneum are easily elicited when carefully looked for.

However, in this communication, I shall discuss only those paradoxical pressure values which are obtained with the pneumothorax needle indubitably located within the pleural space which does not, directly or indirectly, communicate with the abdominal cavity.

Genesis of Negative Intrapleural Pressure. It may not be amiss at this time to refer, even though briefly, to the genesis of the normal negative intrapleural pressure and the rôle played by changes in these pressures in pneumothorax in general, and on the homolateral diaphragm in particular.

The negative intrapleural pressure is developed slowly, and is due directly to the fact that the size of the thorax after birth increases more rapidly, and to a greater extent, than the lungs which it holds.⁴ To fill this enlarging cavity, the elastic lungs expand as far as the bony thorax will permit. Intrathoracic pressure is the pressure exerted on the mediastinal organs, and is equal to atmospheric, less the opposing tension of the elastic recoil force of the expanded lungs. This pressure is obviously more negative during the inspiratory phase, when the lung is stretched to the maximum capacity of the thorax, and less negative during expiration, when the lung has become smaller, and so partially satisfied its own elastic recoil.

When pneumothorax is induced and the pleura and diaphragm are free from extensive adhesions, the lung retracts, and its own elastic recoil is satisfied in direct proportion to the amount of air inflated, with the result that the intrapleural pressure becomes less and less negative. In such cases, the movement of balance, *i. e.*, the pendular movement of the mediastinal contents and under certain circumstances, the paradoxical movement of the diaphragm may be clearly elicited.⁵

Paradoxical Diaphragmatic Excursions in Negative Pressure Pneumothorax. It is still a moot question as to whether or not paralysis of the diaphragm is an absolute pre-requisite for its paradoxical response. I have often seen a raised or motionless diaphragm in cases with complete pneumothorax. Furthermore, an actual ascent of the diaphragm on inspiration is not infrequently observed in cases where the lung fails to expand appreciably, in the presence of highly negative pressures. This paradoxical response has also been noted by Bittrof.⁶

In none of these cases was there any justification for the assumption that the hemidiaphragm involved had been paralyzed. Wellman¹⁴ proved conclusively that the diaphragm in pneumothorax suffers no paresis. On opening the abdominal cavity of rabbits with induced pneumothorax, he saw waves of contraction in the homolateral diaphragm even if its descent on inspiration was hardly discernible. Moreover, he elicited a current of action from the affected leaf during the inspiratory efforts.

It therefore seems reasonable to assume that the efforts of an

enfeebled diaphragm to descend on inspiration in such cases is more than counterbalanced by the rapidly falling intrapleural pressure, with the result that it is aspirated into the involved hemithorax.

Paradoxical Diaphragmatic Response in Positive Pressure Pneumothorax. That the paradoxical response of the diaphragm in pneumothorax cases which were not phrenicectomized may have a different pathogenicity, has been recently pointed out by Udaone and Vadone.⁷ They showed that the basis of the phenomenon is the descent of the diaphragm on expiration in cases with positive pressure during the expiratory phase. At this instant, the diaphragm, on finding itself relaxed, is repelled downward by the positive pressure in the pleural cavity. When it contracts again in the next inspiratory phase, it only rises to the height it attained before the impact of the positive pressure. The ascent during inspiration is therefore apparent rather than real.

Paradoxical Diaphragmatic Response After Phrenicectomy. It is of course different in the case of a paradoxical response in pneumothorax when the homolateral phrenic nerve is severed. Here the inert diaphragm follows the labile mediastinum, and responds in the same fashion as its pendular movement. On inspiration, the lung does not expand rapidly and sufficiently enough to fill the enlarging thoracic cage, with its increasing negative pressure, with the result that the mediastinum (if not fixed) and the diaphragm are sucked into the hemithorax. On expiration, these organs revert to the position they held at rest. The movements just described are not materially influenced by the presence of a moderate pleural effusion.

The Pathogenesis of the Kienboeck Phenomenon. When Kienboeck⁸ in 1898 first described the phenomenon now bearing his name, little was known of the pneumodynamics involved. He assumed, and Stembo,⁹ Holzknecht,¹⁰ Arensperger,¹¹ von Muralt,¹² and De la Camp,¹³ agreed with him, that the paradoxical movement of the fluid in hydropneumothorax was due to the inversion of the diaphragm into the abdominal cavity because of the weight of the fluid it supported. When, during inspiration the diaphragm contracted, it only became flatter, and so raised the fluid level in the thorax. Later, Kienboeck assumed that the diaphragm was paralyzed, and being inert, it was pushed up by the abdominal pressure which increased because of the inspiratory descent of the normal contralateral hemidiaphragm.

In view of the knowledge now available, neither of these explanations help in the understanding of the *modus operandi* of the Kienboeck phenomenon. It has already been shown that the diaphragm is not paralyzed in ordinary pneumothorax. Moreover, inversion of the diaphragm is of very rare occurrence. I have observed but 1 case in over 600 treated with pneumothorax, and this was a patient

who had a recent phrenic avulsion in the presence of a positive pressure pneumothorax.

As to the rôle of the abdominal pressure in unilateral elevation of the diaphragm in pneumothorax or hydropneumothorax, it has been shown by Wellman that no change in the height of the paralyzed or normal diaphragm takes place on the side of the pneumothorax when the abdominal cavity is opened. Moreover, it can be observed radioscopically that pressure applied to the abdomen fails to push the affected leaf of the diaphragm higher up into the chest.

The Kienboeck phenomenon cannot therefore be explained on the basis of the original assumption, but its mechanism can be easily understood if we consider it under the two categories; with and without paralysis of the diaphragm. (1) When the diaphragm is paralyzed it follows the labile mediastinum by being sucked into the chest cavity during the inspiratory phase when the pleural pressure is negative. When fluid is present, the level naturally rises on inspiration and falls on expiration. Moreover, the inspiratory shift of the mediastinum toward the pneumothorax side diminishes the size of the pleural space and thus helps to raise the level of the fluid it contains. (2) With the diaphragm intact, the phenomenon can be observed if the expiratory pressure is positive or the inspiratory pressure highly negative. As already shown, the basic phenomenon of the former is the descent of the diaphragm due to the impact of the positive pressure, at the moment of its expiratory relaxation. The inspiratory ascent is only apparent. When the positive pressure is removed, a loss of the phenomenon ensues. On the other hand, in the presence of a high negative pleural pressure, and only a small effusion, the diaphragm may actually be aspirated into the chest on inspiration, as has already been shown above.

Paradoxical Intrapleural Pressures. The mechanism involved in the production of the Kienboeck phenomenon is stressed because of its importance in the understanding of paradoxical intrapleural pressures. It must be understood that paradoxical diaphragmatic response and paradoxical pleural pressures are not synonymous. As a matter of fact, they do not occur simultaneously, as suggested by Durien,¹⁵ Hamman,¹⁶ Muralt and others, and they have an entirely divergent pathogenicity. Whether the paradoxical movement is due to a paralyzed diaphragm or not, and whether the intrapleural pressure is positive or negative, contrary to the opinion of Parfitt and Crombie,¹⁷ Samson,¹⁸ and others, the pressure relation in the pleural space remains unaltered; *i. e.*, if it is negative on inspiration, it is less negative on expiration, and when positive on inspiration, it is more positive on expiration.

Table 1 shows a study of 11 cases in which phrenic avulsion was performed to augment the effect of a preëxisting pneumothorax.

It will be noted that the negativity of the inspiratory pressure before inflation is not unlike that found in the average pneumothorax case, and the expiratory pressures are invariably less negative. The final pressures at the completion of the refills in such cases, whether positive or negative, retain the normal relations to each other; *i. e.*, the expiratory pressures are either less negative or more positive than those observed on inspiration. In no case was a paradoxical pressure value observed because of the paralysis of the diaphragm.

TABLE 1.—SHOWING NORMAL RELATION OF INTRATHORACIC PRESSURE VALUES AFTER PHRENICECTOMY IN 11 CASES WITH INDUCED PNEUMOTHORAX. PRESSURES ARE IN CUBIC CENTIMETERS OF WATER.

Name.	Sex.	Age.	Pnx. induced.	Side.	Phrenicectomy.	Pressure before inflation.		Pressure after inflation.	
						Insp.	Exp.	Insp.	Exp.
S. T.	F.	29	7-14-29	R.	1- 3-30	-2	+3	-1	+7
A. L.	F.	16	7-24-29	R.	3- 3-30	-6	-4	+7	+9
A. N.	F.	19	10-21-30	R.	1- 7-31	-8	-4	+4	+6
Y. S.	F.	28	7- 6-30	R.	6-11-31	-5	-3	+5	+8
M. F.	F.	17	4- 3-31	R.	8- 3-31	-5	-3	-3	-1
E. T.	F.	28	2- 5-31	L.	4- 3-32	-4	-2	+8	+10
R. M.	F.	32	5- 4-32	R.	4-13-33	-4	-1	+7	+12
L. K.	F.	21	7-20-33	L.	10-10-33	-7	-3	-3	-1
J. S.	M.	34	10-20-31	R.	6-12-34	-5	-3	-2	-0
F. M.	F.	32	6-21-33	R.	10-12-34	-5	-3	+3	+5
J. G.	M.	37	3- 6-34	R.	6-21-34	-5	-3	+1	+2

TABLE 2.—PARADOXICAL INTRAPLEURAL PRESSURES IN 4 CASES TREATED WITH PNEUMOTHORAX.

Patient.	Age	Sex.	Side.	Pnx. induced.	Pressure before inflation.		Pressure after inflation.	
					Insp.	Exp.	Insp.	Exp.
J. S.	25	M.	L.	12-20-27	-6	-2	+16	+12
M. V.	30	F.	R.	9- 4-25	-8	-4	+24	+20
P. F.	29	F.	L.	5- 4-31	-8	-4	+18	+12
A. B.	25	M.	R.	8-13-26	-12	-6	+20	+16

However, in a study of over 600 pneumothorax patients, 4 were found who exhibited unequivocal paradoxical pressure values. In none, as has already been stated, was there the slightest possibility of the needle having entered the abdominal cavity. In none was there a high position of the diaphragm on the side treated. The paradoxical readings have thus far been obtained in 1 case for 4 months, in 2 cases for 2½ years, and in 1 case for over 5 years. No untoward symptoms were observed, and the collapse therapy was

continued in one until its successful termination, and 3 are still receiving inflation.

In none of these were paradoxical pressure readings obtained while the intrapleural pressure was still negative during the early part of the refill. They were noted only when the pressure values in both inspiration and expiration had become positive during inflation. Weinstein, working with Muralt,¹² has had similar experiences.

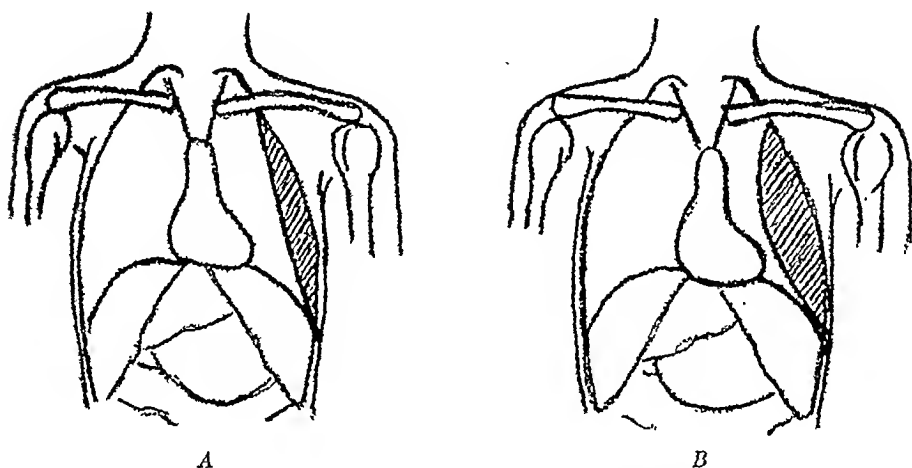


FIG. 1.—(A) Size of pneumothorax pocket decreased because of the stretched pleural limiting membrane in inspiration. (B) Size of pneumothorax pocket increased in expiration when this membrane is relaxed.

The patients showing paradoxical pressure values had a limited pneumothorax, and in all of them fluoroscopy and occasionally radiography disclosed extensive band-like adhesions with a pleural limiting membrane bound to or near the diaphragm below and to the upper part of the chest above. The diaphragm on the treated side was usually bound down by adhesions. The most important feature in these cases was the pleural limiting membrane, which had a convexity toward the mediastinal aspect of the hemithorax. This was best observed fluoroscopically.

It appears that on inspiration after the limited pleural space has been distended by the inflated air under positive pressure, the rising ribs and the descending diaphragm, when its function is not completely destroyed by adhesions, pull on the more or less convex limiting membrane and straighten it out sufficiently to decrease the size of the pneumothorax pocket. The tension of the air enclosed must necessarily rise at that moment. The converse is true during expiration, when the ribs descend and the diaphragm rises to its former position. This permits the limiting membrane to relax and assume its original mediastinal convexity. The size

of the pneumothorax pocket is thus increased and a fall in the pressure of the air it contains inevitably follows.

Summary. 1. The negative value of the intrapleural pressure is due to the fact that the thorax after birth increases more rapidly and to a greater extent than the lungs it holds. It is equal to atmospheric pressure minus the elastic recoil power of the lungs. This pressure is more negative on inspiration, when the lungs are stretched to the maximum capacity of the expanded thorax and less negative in expiration, when the lungs have become smaller and so partially satisfied their elastic recoil.

2. Paradoxical pressure, *i. e.*, less negative values on inspiration as compared with expiration, may be obtained if the needle, instead of entering the thorax, finds its way into the abdominal cavity.

3. Paradoxical intrapleural pressure and paradoxical response of the diaphragm do not occur simultaneously and have an entirely divergent pathogenicity.

4. Persistent paradoxical pleural pressures were obtained in but 4 cases among the 600 treated with induced pneumothorax. They were observed only in limited positive pressure pneumothorax.

5. The most important feature in these cases was the pleural limiting membrane which had a convexity toward the mediastinum. On inspiration, the ascending ribs and descending diaphragm straighten this membrane sufficiently to decrease the size of the pneumothorax pocket, thus increasing the tension of the air it contains. On expiration, the relaxed limiting membrane assumes its original mediastinal convexity, thereby enlarging the pneumothorax pocket. A fall in the pressure of air contained must necessarily follow.

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FAMILIAL PURPURA.

REPORT OF TWO CASES.

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In addition to thrombocytopenic purpura and hemophilia, another group of "bleeders" has been described. These patients give a familial history of bleeding and show an unusual group of blood findings characterized by prolonged bleeding time, normal clotting time, and normal number of platelets. The clot usually retracts but this may be somewhat delayed. Unlike hemophilia, the disease is found in both sexes and may be transmitted by either parent.

The tendency to bleed appears early, is relatively mild, and becomes less severe after adolescence. The most common forms of hemorrhage are epistaxis, bleeding from the gums, and tendency to bruise easily. The literature, however, affords illustrations of practically every known form of bleeding.

Kehrer¹ in 1876 first called attention to this condition; he was followed in 1881 by Hutchinson². No further cases were reported until Hayem³ discussed 3 in 1900. Thirteen years later Austin and Pepper⁴ reported 1 case. Since then the literature has contained many references to this disease (5 to 24).

In order more successfully to study these conditions some exhaustive experiments have been made as to methods and apparatus. We lack space for details but should mention the painstaking work of Morawitz and Jürgens,²⁰ Jürgens,²¹ Jürgens and Naumann,²² and von Willebrand.²³

Recently we have observed two negro boys, brothers, suffering from this hemorrhagic tendency. The bleeding was of the usual type and both patients suffered at times from secondary anemia. The bleeding time was usually prolonged. The platelets appeared to be normal and only once were they found to be low. In one the retractability of the clot was delayed; in the other it was normal. The clotting times remained always within normal limits. We were not able to demonstrate positive tourniquet tests. In both boys the tendency to bleed is gradually diminishing.

Case Reports. CASE 1.—D. M. (No. 255087), a 9-year-old negro boy, was first admitted to this hospital on February 21, 1923, complaining of bleeding gums.

There was no family history of hemorrhagic diathesis. His younger brother (whose case is described in detail below) had at this time shown no signs of bleeding. One brother and 2 sisters had died in infancy of unknown causes.

Only illness was measles in early infancy.

The parents stated that from babyhood the patient had bled from the gums, and following any injury. Epistaxes frequently accompanied head colds, and after severe hemorrhages hyperpnea had been noticeable. During the year previous to admission, tarry stools had been observed.

He had been in the hospital (Wilmington, N. C.) 9 months previous to entry for weakness and shortness of breath. He improved rapidly after transfusion. For the following 9 months bleeding from the gums had been constant.

Physical Examination. A thin boy, moderately ill. Weight, 64 pounds. The cervical glands were moderately enlarged. Marked pallor of the mucous membranes and nail beds. Fundi were normal. The gums were ecchymotic, with some fresh oozing. Caries of the teeth. The tonsils were moderately enlarged. The lungs were clear. The heart enlarged to the left, and a rough systolic murmur was heard over the precordium, maximum at the apex, and transmitted to the axilla. The blood pressure was 112/70. The spleen was not palpable. The urine was normal.

Blood: hemoglobin, 41%; red blood cells, 3,720,000; white blood cells, 6200; with normal differential count. The red blood cells showed central pallor. The blood platelets were 200,000 per c.mm. The clotting time was 9 minutes, control 2 minutes. The patient bled freely for 30 minutes, after which the bleeding was stopped by pressure. The fragility of the red cells was normal. The blood Wassermann reaction was negative. Blood culture: no growth. Roentgen ray and fluoroscopy of the heart revealed moderate enlargement.

The patient remained in the hospital about 2 weeks, improved somewhat, but the gums continued to bleed, local applications of thromboplastin giving only temporary relief.

During the next 2 years that the patient was followed in the medical clinic, the red cell count varied from 3,350,000 to 4,240,000; the hemoglobin from 46 to 56%; the white cell count from 1850 to 7050. Platelet count was 306,000. Bleeding from the gums, though variable in severity, was almost continuous. Thromboplastin was applied to the gums with variable success. Once two petechial hemorrhages were noticed in the conjunctiva of the left eye.

On February 2, 1925, the patient was readmitted because of severe bleeding from the gums.

The physical findings were much as on his previous admission. He weighed 89½ pounds. Pallor was marked. The teeth were dirty. There

were two small ecchymotic areas on the buccal mucous membrane which bled on pressure. There was moderate general glandular enlargement. The spleen was palpable.

The urine was normal; the stool negative for occult blood. Hemoglobin, 30%; red blood cells, 1,800,000; white blood cells, 3800 with normal differential; platelets, 40,000; clotting time, 4 minutes; bleeding time, more than 35 minutes.

He received 3 direct transfusions, the amount of blood varying from 350 to 500 cc. Fibrinogen and thromboplastin were applied to the gums. Except for a brief transfusion reaction the course was afebrile throughout. The gums continued to bleed, but on discharge the hemoglobin was 50%, the red cells, 3,100,000.

After being followed for 3 months in the dispensary, the patient disappeared for 5 years.

During the interval before his third admission, May 6, 1930, he had visited St. Luke's Hospital, and the Morrisania Hospital (both in New York), and received 6 transfusions. In the 9 months previous to entry he had lost 21 pounds, was weak, pale and inactive. The gums bled constantly, and evening rises of temperature had been common. The day before admission he had a mild epistaxis.

On examination the boy appeared to be acutely ill, dyspneic and drowsy. Temperature was 104°, pulse 128. The mucous membranes were almost white. The fundi were normal, eyelids slightly edematous. The gums were pale, hypertrophic, and soft, with a marked tendency to bleed. Lungs: scattered râles at the lung bases. The heart was markedly enlarged with accentuated pulmonic second sound and a systolic murmur, as formerly observed. The liver was slightly enlarged, spleen just palpable.

Hemoglobin 9% (this is very low for accuracy. The next day, after a transfusion of 700 cc., the same observer made it 24%); red blood cell, 1,370,000; white blood cells, 6350, with normal differential; the red cells showing marked variation in size and shape. The platelets were 380,000; bleeding time, 10½ minutes; clotting time, 6 minutes, with a retractile clot. No sickle cells were found in a wet preparation. The fragility of the red cells was normal. No increase in the serum bilirubin. Blood calcium 9.7 mg. per 100 cc. The urine and stools were normal.

After being afebrile for 3 weeks, he developed a lobar pneumonia (right lower lobe). The predominant organisms in the sputum were hemolytic staphylococcus aureus, and streptococcus viridans; no tubercle bacilli found. The leukocytes rose to 15,000 with 89% neutrophils. Recovery was uneventful. He received 6 direct transfusions: one of 500 cc. the others of 700 cc. each.

While the bleeding never stopped entirely, some improvement was noticed after each transfusion. Local treatment of the gums was unsatisfactory. The red blood cells rose to 3,410,000; the hemoglobin to 55%. The bleeding time varied from 2½ to 10 minutes. The platelets varied from 190,000 to 380,000, except for one count of 40,000.

The patient was discharged after 2½ months.

The next 2½ months were characterized by striking improvement. The weight rose to 133½ pounds. Hemoglobin, 82%; red cells, 4,300,000. Efforts to have some much needed dental work done were frustrated by his mother. Moderate bleeding continued. Liver extract and iron ammonium citrate were prescribed.

His fourth admission (October, 1930) was for severe bleeding from the gums. A stay of only 10 days was uneventful. The red cells varied from 3,100,000 to 4,000,000; the hemoglobin from 66 to 68%, the bleeding time was more than 30 minutes, the platelet count 300,000. The physical and laboratory findings were unchanged.

During the 4 years that have elapsed since his last admission the patient has been followed in the dispensary. Bleeding from the gums has been intermittent, though never severe. The mother has never permitted much dental work to be done. Iron ammonium citrate has been given almost continuously, the hemoglobin has varied from 50 to 90%; the red blood count from 3,800,000 to 5,000,000; the clotting time from 2 to 5 minutes; the bleeding time from $1\frac{1}{2}$ to $9\frac{1}{2}$ minutes; and the platelets from 101,000 to 263,000. He has grown and matured normally. His weight was 151 pounds when last seen. He is now over 21 years old.

CASE 2.—O. M. (No. 254687), the brother of Case 1, was first admitted to this hospital on May 8, 1930. He was 15 years old, and had been bleeding from the gums for 8 or 9 days.

In childhood he had measles, mumps, and scarlet fever. Always had epistaxis with a cold. He had grown normally and at the time of admission was in high school. In December, 1928, he was admitted to St. Luke's Hospital, New York, with a history of hematuria and of slight bleeding of the gums (an abstract of this admission was very kindly furnished us by St. Luke's Hospital). The urine on admission showed gross blood. Roentgen ray of the kidneys were negative. The Wassermann reaction was negative. Hemoglobin, 86%; red cells, 4,500,000; white cells, 6800, with normal differential; platelets, 170,000; bleeding time up to 20 minutes, clotting time from 5 to $6\frac{1}{2}$ minutes. One transfusion of 250 cc. Recovery was uneventful, and the boy left after a month.

Ten days before admission to Presbyterian Hospital he had developed a head cold which was accompanied by vomiting and by a severe nose bleed. A day or two later his gums began to bleed; this continued up to the time of entry. Just before admission he had anorexia, frequent vomiting, moderate epigastric pain, occasionally tarry stools and increasing pallor. His left ear had been discharging for 6 weeks.

Physical Examination. A colored boy, aged 15, moderately ill. Temperature, 100.8° ; weight, 115 pounds. Marked pallor of the mucous membranes and of the nail beds. There was a purulent discharge from the left ear. The gums were hyperplastic, pale, friable and bleeding. Teeth were in fair condition, some gingivitis. Tonsils large with prominent crypts. Moderate enlargement of the heart, and systolic murmur could be heard over most of the precordium. Liver edge palpable, two finger-breadths below the costal margin. The spleen was just palpable.

The urine was normal. The Wassermann reaction negative. Hemoglobin, 30%; red blood cells, 2,230,000; white blood cells, 8100, with normal differential. Platelets, 260,000. Bleeding time very greatly prolonged, clotting time was only 3 minutes, retraction of the clot did not begin until after 20 hours. The fragility of red cells was normal. The serum bilirubin was normal. The guaiac test on the stool was 1+. The blood calcium was 10.3 mg. per 100 cc. Hemolytic streptococci were grown in pure culture from the gums.

Two days after admission a direct transfusion of 700 cc. was given. Treatment included ferric ammonium citrate and liver extract. He ran fever for 10 days. The gums improved strikingly, after 16 days they bled very little, red cells rose to 4,180,000, with a hemoglobin of 55%.

During the next $2\frac{1}{2}$ years he was seen infrequently in the dispensary. The hemoglobin varied from 89 to 95%, the red cells from 4,800,000 to 5,100,000. Bleeding time from $5\frac{1}{2}$ to 3 minutes; clotting time remained normal. Moderate oozing from the gums continued. He gained from 117 pounds to 161 pounds. The boy matured rapidly and improvement in his general condition seemed to keep pace with this gain. He visited the dental clinic frequently. The bleeding from the gums was not severe enough to interfere with this work. During this period his hemoglobin varied from

58% to 82%, his red blood count from 4,100,000 to 5,100,000, and his platelets from 169,000 to 238,000. On one occasion his bleeding time was 8 minutes, his clotting time $1\frac{1}{2}$ minutes.

He has not been seen in the clinic since May, 1933.

In reviewing these 2 cases we feel no elation because of gratifying results. Although both boys grew and developed normally, when last seen both had hemoglobins in the neighborhood of 50%; in other words, our therapy left much to be desired. We feel justified in thinking some of the responsibility rests with the patients. As example of their mental attitude and lack of coöperation we mention one instance that is noteworthy: they could never go to the dentists when the moon was full, because at such time the bleeding was worse!

Comment. In adding 2 cases to the already large group, it is not our intention to attempt a new classification, or to propose a new etiology.

A review of the literature reveals many cases which fit into a definite pattern, characterized by an hereditary bleeding tendency, associated with prolonged bleeding time. The clot retraction is generally delayed or absent while the clotting time and platelet count are both within normal limits. The hemorrhagic tendency may be transmitted by either parent to children of either sex.

The fact that some of the cases have shown thrombocytopenia, but are linked to this group by their familial characteristics, demonstrates the absence of distinct borderline between this disease and true purpura hemorrhagica. The occurrence of a similar type of bleeding in female members of families, the male members of which have had hemophilia, suggests a possible link with that disease. On the other hand, sporadic cases in every way similar to the disease we are describing have occurred in which no family history of bleeding could be found.

Most of the evidence points to a functional insufficiency of the platelets as the etiologic agent. Definite morphologic changes in the platelets have been noted.

In one group of cases recently described, the platelets were morphologically normal, but were unable properly to agglutinate and produce a normal clot. The final word regarding the etiology has certainly not been written.

In view of the generally good prognosis, therapy should aim to control the immediate hemorrhage, and to combat the resultant secondary anemia.

For both purposes transfusion has proved a valuable weapon. Hemostatic substances applied locally are of doubtful value. General measures such as adequate rest when bleeding is severe, removal of foci of infection, and liberal doses of iron and liver seem to help materially. Irradiation of the spleen may be of value, but splenectomy is definitely contraindicated.

Summary. 1. Two cases have been described of a familial, chronic, hemorrhagic diathesis; with prolonged bleeding time, but with normal clotting time, and normal platelets.

2. The term "Hereditary Thrombasthenia" is usually employed to describe this syndrome, but recently "Constitutional Thrombopathy" has been suggested.

3. Treatment should be conservative: symptomatic local therapy and measures to combat the anemia. Splenectomy is contraindicated.

4. The bleeding tendency usually manifests itself in infancy or childhood. If the patient successfully passes through what may be termed the critical stage (up to 15 years), the prognosis is excellent.

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BOOK REVIEWS AND NOTICES

THE KIDNEY IN HEALTH AND DISEASE. Edited by HILDING BERGLUND, M.D., Stockholm, Sweden. Formerly Chief of the Department of Medicine at the University of Minnesota, and GRACE MEDES, PH.D., Research Biochemist in the Lankenau Hospital Research Institute, Philadelphia. With the Collaboration of G. CARL HUBER, M.D., Professor of Anatomy and Director of Anatomical Laboratories and Dean of the Graduate School of the University of Michigan, WARFIELD T. LONGCOPE, M.D., Professor of Medicine in the Johns Hopkins University, Baltimore, and ALFRED N. RICHARDS, PH.D., M.D., Professor of Pharmacology in the University of Pennsylvania, Philadelphia. Pp. 754; 163 illustrations. Philadelphia: Lea & Febiger, 1935. Price, \$10.00.

THIS volume represents a collection of papers on normal and pathologic function and structure of the kidney. Nearly all of these papers, most of them now in revised and amplified form so as to bring them up to date, were originally presented by 41 clinical and laboratory investigators at a symposium which took place in Minneapolis during the summer of 1930.

The subject matter of the book is divided into six parts: Anatomy and physiology of the kidney (Chapters 1 to 9); clinical aspects of renal functions (Chapters 10 to 17); Bright's disease and various other pathologic renal conditions (Chapters 18 to 26); albuminuria and edema (Chapters 27 to 36); ocular changes in Bright's disease (Chapters 37 and 38); and clinical aspects of Bright's disease (Chapters 39 to 44).

The work contains a wealth of information and will be of much value to students of the kidney. Of particular excellence is the part dealing with kidney function. In no other book is there gathered in such accessible form so complete a survey of renal physiology by men largely responsible for the advances made; it must suffice to cite as examples the papers by Richards, Marshall, Rehberg, Homer Smith and White. The various tests for renal function and the pathologic physiology of renal insufficiency form the contents of the second part of the book. Further examples of outstanding contributions are the papers of Longcope and his associates on the part played by streptococci in the establishment of nephritis, by Leiter on nephrotic edema, and several papers by Franz Volhard who together with Fahr laid the foundation of the modern concept of Bright's disease.

B. L.

DAS EXTREMITÄTEN-, THORAX- UND PARTIAL-ELEKTROKARDIOGRAMM DES MENSCHEN. Eine Vergleichende Studie. By PROF. DR. FRANZ MAXIMILIAN GROEDEL, Direktor des William C. Kerckhoff-Herzforschungsinstituts zu Bad-Nauheim. Band 1: Text (358 pages; 334 illustrations); Band 2: Atlas with 200 Plates. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 25.

THE author, the well-known former director of the Nauheim Institute, but now writing from New York, tells us that after almost 25 years of study he has succeeding in isolating the "Partial-electrocardiograms" of the left and right heart. Though still lacking postmortem confirmation of his clinical studies, he regards this monograph as the first fruit of this new method.

These partial electrocardiograms are given as quite different from Lewis' dextro and levograms for reasons that cannot be detailed, much less evaluated, here. Einthoven's triangle of forces is also rejected in theory, though occasionally used for practical didactic purposes. As an example of the lines of approach eight critical points on the heart are selected with the aid of special, movable "Tastelectroden." Increased distance from points 1 to 4 (in the right ventricle) or 5 to 8 (in the left) indicate delay in excitation spread; an abnormally high site for points 2 or 6 indicate increased speed of spread and so on. The monograph aims to demonstrate that the electrocardiogram records the result (summation or neutralization) of lines of potential developed simultaneously in the two ventricles. Its form therefore, is influenced by the amount of rotation of the heart as well as by the direction of its anatomical axis, and cannot be taken as an expression of the course followed by the contraction impulse. The dextro-electrocardiogram appears normally to have large *R* and *S* waves, the sinistro-electrocardiogram a *q* wave (synchronous with the *R* of the right ventricle), a large *R* (synchronous with the right *S*) and a slightly delayed *T*.

These are indeed weighty considerations for cardiac specialists and students of the cardiac mechanism. If the author is correct, and his great experience entitles him to the most careful consideration, much that is now accepted by cardiologists will have to be revised. It is hardly necessary, then, to recommend to serious students of the subject the careful study of this book that its text requires.

E. K.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 406; 55 illustrations including 2 plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, \$5.00.

It is not surprising that the extensive and productive studies in this important field have required a new edition of this book in the short space of 2 years. Especially has the pituitary, with its numerous interrelationships, been a fallow field, so that some 78 pages are required to cover its "recent advances" with due regard for a proper background. The parathyroids, of course, have assumed more important proportions, while the hypoglycemic phases of insulin action also require more space than ever before. The pineal, on the other hand, gets but scant notice and Rowntree's thymic precocity was apparently included at the last moment. Collip's antihormones and the complicated topic of endocrine interrelationships are conservatively handled in Chapter 9. When today's newly discovered facts are crowding so much of the medical knowledge of yesterday either to the scrapheap discards or to the uninteresting category of truisms, such well-digested surveys as this should prove highly useful to the physician who continues to be a medical student.

E. K.

THE HARVEY LECTURES. Series 29. Delivered under the Auspices of The Harvey Society of New York, 1933-1934. Under the patronage of the New York Academy of Medicine. By Doctors R. E. DYER, W. M. CLARK, R. G. HARRISON, E. A. DOISY, E. A. GRAHAM, C. L. STREETER, T. M. RIVERS and D. W. BRONK. Pp. 262; illustrated. Baltimore: The Williams & Wilkins Company, 1935. Price, \$4.00.

This volume is preceded by a short, but singularly penetrating, minute on the death of the President of the Society, Alfred Hess. The eight lectures here collected are of an unusually high quality even for this series. No one

could contest the modest statement in the Preface as to "the distinguished rôle which they fill in Medicine in New York City." Distinctions would be invidious between such sterling presentations as Dyer's typhus fever, Clark's oxidation-reduction systems, Harrison's heteroplastic grafting in embryology, Doisy's estrogenic substances, Graham's clinical studies of the biliary tract and of the pancreas, Streeter's morbid processes in the fetus, Rivers' filterable viruses and Bronk's nervous mechanism of cardiovascular control.

E. K.

FAILURE OF THE CIRCULATION. By TINSLEY RANDOLPH HARRISON, M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. Pp. 396; 60 figures and 22 tables. Baltimore: The Williams & Wilkins Company, 1935. Price, \$4.50.

THE conventional title of this book covers a fresh, important approach to an old problem—namely, the study of such hemodynamic states as "the dyskinetic syndrome" by modern methods that are still apt to be more familiar to the physiologist and biochemist than to even the well-trained clinician. The author's training in and use of these methods, combined with his predominant interest in the clinical problems, peculiarly qualifies him for a study which has led to new interpretations of a number of the clinical manifestations of heart disease. In "hyperkinetic" conditions the author includes such conditions as the overactive or soldier's hearts and those cases where "the physiologic subjective and objective phenomena of circulatory activity appear in exaggerated form." In the "hypokinetic" group are the various shocks and collapses of acute circulatory failure with decreased response. "Dyskinetic" refers to conditions of or leading to congestive heart failure, *i. e.*, hardly more specific than "organic heart disease." The attempt is made to bring the general circulatory disturbances (not including angina pectoris, which is regarded as a local disturbance) into these three categories. The author has attained a good measure of simple clearness without dogmatism. Thus many problems, unanswerable to-day, are left unanswered. However, Hope's "back-pressure" hypothesis of cardiac failure and oxygen lack in the heart muscle as the underlying functional disturbance in angina pectoris and coronary thrombosis are clearly supported. Thyroidectomy in the treatment of heart disease is presented but regarded as too recent to be evaluated—altogether a fresh, sane, useful book.

E. K.

MAIMONIDES (THE RAMBAM). THE STORY OF HIS LIFE AND GENIUS. Octocentennial Edition. By DR. J. MÜNZ. Translated from the German, with an Introduction, by HENRY T. SCHNITTKIND, Ph.D. Pp. 238. Boston: Winchell-Thomas Company, 1935. Price, \$1.50.

THE accompaniment of the two earlier persecutions of the Jews by the incorporation of their best thoughts in the Bible and the Talmud respectively have suggested to the anonymous promoters of the "Jewish Bookshelf" that the present "persecution" should be accompanied by a third collection including the best thoughts of the past. This account of Maimonides, coming appropriately on his 800th anniversary, is the first of the series. The 100 books ranging from philosophy to fiction, that are to be published at the rate of 5 volumes a year, should constitute a treasure house of value to Jew and Gentile alike.

This highly eulogistic account of Moses ben Maimon is properly concerned chiefly with his rôle as a philosopher and religious commentator. We read also of his life in the Jewish community in Egypt, where his family settled after being driven from Spain to North Africa and the Holy Land, and of his

display of practical qualities of leadership in raising their intellectual standards and bringing together the warring factions of Judaism. This leadership, it seems, descended in his family for more than 10 generations. As court physician to the Sultan Saladin, his medical side came into prominence. Though trained in the Arabian school, he seems to have been a worthy follower of Hippocrates, using reason based on experience as his guide. The cure should be as simple as possible; the best one can do is to help Nature by fortifying the patient's strength; alcohol is bad for the young but food for the old (one of his 22 rules of hygiene in the *Mishneh-Torah*). Of the 8 medical treatises referred to, we would note especially his book on Psychiatry, called forth by his treatment of the Sultan Almalik's melancholia, and his Epitome of Medicine, a summary of Galen and of the history of medicine up to his time. On reviewing his colorful and versatile life, we agree that he stands out with Richard and Saladin as a 12th century leader and as one of the greatest Jews of the Christian era.

E. K.

SOME NOTABLE EPIDEMICS. By H. HAROLD SCOTT, M.D., F.R.C.P. (LOND.), D.P.H., D.T.M. and H. (CAMB.), F.R.S.E., Assistant Director, Bureau of Hygiene and Tropical Diseases. With a Preface by W. W. JAMESON, M.A., M.D., F.R.C.P., Barrister-at-Law, Professor of Public Health in the University of London; Dean of the London School of Hygiene and Tropical Medicine. Pp. 272. Baltimore: William Wood & Co., 1934. Price, \$4.75.

THE careful manner in which this work was planned raises it well above a mere account of various "classical" English epidemics which are not to be found in Hirsch, Hecker or Creighton. Twenty-two epidemics occurring since 1850 have been selected both to illustrate particular landmarks in public health work (such as the first use of chlorine as a water disinfectant or of pasteurization of milk) and to demonstrate how specialists viewed epidemics in pre-bacterial days. A chronological order has been largely followed, with occasional exceptions in order better to compare epidemics caused by the same mode of conveyance (water, milk, food, contact and so on). It is indeed surprising how the keen insight of John Snow, for instance, could grasp the essentials of cholera spread in 1854, and outline steps to be taken which have been but little improved since his day. Eleven of the epidemics were of typhoid, both water and milk borne, and from infected oysters; 5 of scarlet fever; and 3 of Sonne's dysentery, the last of which occurred in 1933. Though of chief interest, in fact a virtual necessity, to students of public health, these "detective stories" should make interesting reading for most anyone, and profitable reading as well for most any physician.

E. K.

A TEXTBOOK OF BIOCHEMISTRY. Edited by BENJAMIN HARROW, Ph.D., Associate Professor of Chemistry, The City College, College of the City of New York, and CARL P. SHERWIN, M.D., Sc.D., Dr.P.H., LL.D., Member of the Staff of St. Vincent's Hospital, and French Hospital, New York. Pp. 797; 52 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, \$6.00.

THIS book, written by 30 specialists in various fields of biochemistry, is an excellent survey of present-day knowledge. Aside from subjects usually included in textbooks on biochemistry there are chapters on the physico-chemical properties of the living cell, on the chemical processes concerned in resistance and immunity, and on the chemistry of bacteria. The articles throughout the book give evidence of careful condensation of subject matter; the essentials are clearly and thoroughly presented; for those who

would go deeper there are extensive and well-selected lists of references. Some of the chapters dealing with broad subjects (as for example those on the carriage of blood gases, and on oxidations and reductions) conclude with well-written summaries which should prove of particular help to the non-specialist. The editors and contributors are to be congratulated on providing a book which will serve as a good text for the student and as a modern reference volume for the trained worker in medicine, chemistry and biology.
B. L.

THE TREATMENT OF RHEUMATISM IN GENERAL PRACTICE. By W. S. C. COPEMAN, M.A., M.B., B.Ch. (CANTAB.), M.R.C.P. (LONDON), Hon. Physician, B.R.C.S., Clinic for Rheumatism, Peto Place; Assistant Physician, West London Hospital, Children's Department and Hospital of St. John and Elizabeth, etc. With a Foreword by SIR WILLIAM HALE-WHITE, K.B.E., M.D., F.R.C.P., Hon. LL.D., Consulting Physician to Guy's Hospital, etc. Pp. 228. Second Edition. Baltimore: William Wood and Co., 1935. Price, \$3.25.

THIS survey of the numerous methods of treatment used in the various "rheumatic" diseases is remarkably informative and inclusive. To the American physician, whose skepticism about many remedies especially the proprietaries has progressed further than his British cousins, some recommendations may appear uncritical. However, the author's wide experience must be held in mind and his general attitude of optimism in handling these difficult cases—each as an individual and not by rule of thumb—will be useful to many a perplexed practitioner who has the good fortune to have this book fall in his hands.
E. K.

ALLERGISCHE DIATHESE UND ALLERGISCHE ERKRANKUNGEN. By HUGO KÄMMERER, M.D., Professor at the University of Munich; Chief Physician of the Division of Internal Medicine of the Nymphenburger Krankenhaus, Munich, Germany. Pp. 359; 4 illustrations. Second edition, enlarged and improved. Munich: J. F. Bergmann, 1934. Price, Paper, Rm. 26; Bound, Rm. 29.60.

THIS is undoubtedly the best, indeed the first adequate, German text dealing with present-day views of this rapidly developing field. In addition to an extensive clinical and investigative experience the author brings to his subject a wide knowledge of its literature and a sound judgment in evaluating the material. The allergist will find the work a valuable addition to his library, and German-speaking practitioners as well as allergists should consider it indispensable. (Inadvertently the author cites Coca, Walzer and Thommen's "Asthma and Hay Fever in Theory and Practice" as a British, not an American, publication.)
R. K.

DEUTSCHE VOLKSMEDIZIN. Wissenschaftliche Heilkunde und Kultur. By PAUL DIEPGEN, O. Prof. Dr. Med. et Phil., Berlin. Pp. 136; 7 illustrations. Stuttgart: Ferdinand Enke, 1935. Price, Geh. Rm. 6.—; Leinen geb. Rm. 7.40.

Folk medicine, which persists to a surprising and unappreciated extent in all civilized countries, is regarded by the well-known author of these lectures as a particular appropriate study in times of need and sickness, when "art, science and reason so often leave us in the lurch." The historical relationships of the magic and religious needs of the German common folk to scientific medicine and to culture in general are well brought

out in 9 chapters that cover semichronologically the whole of German folk medicine from prehistoric to modern times. The influence of commerce and racial combination with surrounding countries is objectively considered; anti-Jewish measures are traced back to 692! The crusades, the medieval pandemics of body and mind, printing, Paracelsus and Mesmer are important landmarks on the progress toward a modern goal that the author regards as a desirable combination of the good to be found in both folk and scientific medicine.

E. K.

GESCHICHTE DER PHYSIOLOGISCHEN CHEMIE. By DR. FRITZ LIEBEN, Privatdozent an der Universität Wien. Pp. 741. Wien: Franz Deuticke, 1935. Price, M. 20.

THIS work, the first comprehensive history of physiologic chemistry in English, is a studious compilation of detailed information, with an entirely factual presentation. The obvious effort to produce an all-inclusive work—an effort which for physiologic chemistry is almost futile even in the space of 700 large pages—has resulted in a distinctly textbook appearance. This impression is strengthened by the inclusion of countless organic structural formulas, the citation of last-minute researches and the absence of any portraits which might have served to relieve the reader.

From the standpoint of history, the ancient phases, for a book of this size, appear slighted. No effort has been made, for example, to look critically into the history of urea. The credit for the discovery is given to Rouelle the younger, whereas Boerhaave and probably Pott deserve the plaudits in this connection. Far too sketchy also is the author's treatment of "methods," which have always played an undeniably important rôle. Historically, the development of proper blood sugar methods is as important as the discovery of insulin.

In spite of these criticisms, perhaps unavoidable in a pioneer work, much information has been gathered and stored. The work may well serve as a source of reference and as a starting point for future critical histories of the subject which will no doubt appear.

D. D.

MEDIZINISCH-CHEMISCHE BESTIMMUNGSMETHODEN. Eine Anleitung für Studierende der Medizin und für Laboranten. By KARL HINSBERG, Vorsteher der Chemischen Abteilung des Pathologischen Instituts der Charité, Berlin, Privatdozent an der Universität, Berlin. Volume 1. Darstellung der allgemein gebräuchlichen und der wichtigsten quantitativen Methoden. Pp. 93; 29 illustrations. Berlin: Julius Springer, 1935. Price, Rm. 4.80.

THIS small volume is apparently the first part of a work on chemical methods to be used in a hospital laboratory. The first half presents the most used and important general methods and instruments, such as balances, centrifuge, titration, indicators, colorimeters, nephelometers, photometers, polarization, refractometers, gas analysis, blood sampling and nitrogen determinations. In the second special part, the various inorganic (calcium, chlorids, gastric contents, urinary ammonia, alkali reserve) and organic methods are given both in principle and in details of technique. The organic chapter covers hemoglobin, total and residual N, uric acid, bilirubin, blood sugar, cholesterol, acetone, diastase and so on. Much is sacrificed to attain a brief handiness; for non-Germans greater convenience will doubtless be found in works in English, even though larger and more complete.

E. K.

TREATMENT BY DIET. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Instructor in Medicine, Northwestern University Medical School, Chicago; Formerly Consulting Physician, The Mayo Clinic. Pp. 615; illustrated. Philadelphia: J. B. Lippincott Company, 1934. Price, \$5.00.

A PRACTICAL presentation of the subject for the general practitioner. Part I deals with diet requirements in health. In Part II is described the technique for working out the details of a diet prescription as to quality and quantity, with some useful data on comparative servings of various foods. This part is rather well illustrated. In Part III the diet indications in various diseases are taken up, with a brief theoretical discussion and numerous diet lists. Parts IV and V include lists for routine hospital diets, tube feeding; a number of food, weight and other tables; recipes.

R. K.

LA VIE MÉDICALE AUX XVI^E, XVII^E ET XVIII^E SIÈCLES. By DOCTEUR PAUL DELAUNAY, Membre de la Société Française d'Histoire de la Médecine. Pp. 556; 114 illustrations. Paris: Editions Hippocrate, 1935. Price, 40 francs.

THIS thoughtful survey of medical life in the three most important centuries of French history is the fourth production of the Collection "Hippocrate." (Those that have already appeared are: "Acupuncture et médecine chinoise vérifiées au Japon," by T. Nakayama; "l'Atomistique," by M. Boll; "Joseph Le Bon," by Y. Dhotel.) This "para-medical" collection aims to include a wide variety of topics—essays on medical doctrines, the relations of medicine to her sister sciences, medical history, psychological studies and so on.

If the present volume is a true guide, the series should prove interesting and valuable. Here we have presented by an accomplished medical historian chapters on each of the various aspects of medical life; preparatory, private, professional, corporate, religious, political, social, intellectual and doctrinal. Though the story is limited to France, the author offers such a wealth of colorful detail that the sequential flow of the narrative sometimes is impeded. The factual gain, however, more than recompenses, especially as it is reinforced by copious illustrations and a full index of names. The absence of a subject index is the more keenly felt.

E. K.

CLINICAL LABORATORY METHODS AND DIAGNOSIS. A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories, Gradwohl School of Laboratory Technique, and Laboratories, St. Louis County Hospital, etc. Pp. 1028; 328 text illustrations and 24 color plates. St. Louis: The C. V. Mosby Company, 1935. Price, \$8.50.

THIS is one of the most complete and practical books of its kind that we have had the good fortune to meet, and, as one should expect from a Director both of laboratories and a school of laboratory technique, unmistakably clear and concise directions are given for the most varied methods. In few books of this kind, for instance, would one find 15 paragraphs on the Culture of Sterile Maggots for Use in Therapy, with accurate directions for care of eggs, breeding of larvæ and fly colonies and so on. To the blood, that "ganz besondere Saft," is rightly given the major space—262 pages—so that, as well as the customary items, such matters as platelet counting, Schilling hemograms and so on can be treated in some detail. As perfection is as desirable as it is unattainable, attention may be called to the antiquated classification of chronic renal disease, the omission of Wiseman's

diluted plasma method of estimating erythrocyte resistance, the obsolete clinical evaluation of direct and indirect van den Bergh tests, and the fallacious weak point in Wright's platelet theory (platelets should not be expected in the bone marrow, as the pseudopods break off in the vascular channels). Surprising also is the anachronistic reference (p. 933) to Prof. W. G. MacCallum of Columbia! Other slips could be detailed, but they are relatively trifling in a book that conveys such a wealth of accurate information, well presented and copiously illustrated. Especially pleasing are the 24 color plates, expensive items which have almost disappeared from American medical periodical literature. Fifty pages of the blood findings in various diseases should be especially useful to the practitioner. Chapters on autopsy methods, tissue technique, preparation of museum specimens and toxicologic technique add further to the value of this excellent production.

E. K.

THE EVALUATION OF SYMPTOMS. Offered After Fifty Years in Medicine.

By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., Professor of Therapeutics, Emeritus, and formerly Clinical Professor of Medicine, Yale University. Pp. 163. New Haven: Yale University Press for the Author, 1935. Price, \$3.50.

IMPRESSED by the present-day dependence on laboratory methods, the author aims to emphasize the importance of history taking and the study of symptoms. We do not believe, however, that this laudable purpose is to be advanced by the method here followed. A single page on "The Germs of Infection" and the disease they cause can only be trite and incomplete, while the subsequent pages on "Reportable Diseases and Quarantine," and a later section on "Dieting," are irrelevant. A long chapter on "Symptoms of Disease," arranged alphabetically, occupies three-fourths of the book; but this also fails in its aim. Starting with three conditions (acetonuria, agranulocytosis, albuminuria), for which the reader is referred to other pages, the list soon reaches "blood." Here in 12 pages, anemia, monocytes, platelets, chlorosis, leukocytosis, pernicious anemia, leukemia and so on are touched upon in a random and necessarily inadequate manner that does not emphasize the value of the study of symptoms and may deflect the reader from more statements elsewhere. We can only hope, then, that in another edition the author will recast his text so as to bring out more forcibly the valuable lesson for the present generation that lies in the proper evaluation of symptoms.

E. K.

THE TREATMENT OF FRACTURES. By DR. LORENZ BÖHLER, Director of the Hospital for Accidents, Vienna; Lecturer on Surgery in the University of Vienna. Pp. 578; 1059 illustrations. Fourth English edition, translated from the fourth enlarged and revised German edition by ERNEST W. HEY GROVES, M.S., M.D., F.R.C.S., Consulting Surgeon, British General Hospital; Emeritus Professor of Surgery, University of Bristol, etc. Baltimore: William Wood & Co., 1935. Price, \$12.00.

"IN main essentials the fourth German edition, of which this is a translation, follows the same lines as those of the third. . . . The new material in the English edition deals: (1) With the anatomic conditions and the treatment of fractures and fracture-dislocations of the cervical spine, which have been revised in the light of recent experience. (2) In the chapter on medial fractures of the neck of the femur, the recent developments of Sven Johansson's method and the use of two sets of Roentgen ray apparatus for the orientation of the wire guides have been elaborated, because it has been found that in this way the operation is simpler, quicker and more accurate.

As the results of the treatment of fractures depend not merely upon the use of certain appliances and methods, but even more largely upon the education of the surgeon and the organization of the clinic, an Appendix has been added dealing with this important aspect of the problem. For the sake of simplicity, certain other subjects have been relegated to appendices, so as not to break the main theme of the treatment of fractures. These deal with statistics, normal and abnormal movements of the knee-joint, and the nature and treatment of deformities of the foot." (From the Translator's Preface.)

EMOTIONS AND BODILY CHANGES. A Survey of Literature on Psychosomatic Interrelationships 1910-1933. By H. FLANDERS DUNBAR, M.D., PH.D., Departments of Medicine and Psychiatry, Columbia University. Pp. 595. New York: Columbia University Press, 1935. Price, \$5.00.

THIS volume represents the combined labors of Dr. Dunbar and her collaborators under the auspices of the Josiah Macy, Jr., Foundation in the collection and recension of contributions published in the last quarter century dealing with the interrelations of the emotions and the body. The text is divided into three principal parts. Part One, "Orientation and Methodology" presents a critical review of the current psychologic concepts and of the experimental approaches in the fields of biology, internal medicine and medical psychology, to the problem of psychosomatics. Part Two, "Organs and Organ Systems," is devoted to the task of orienting the abstracted materials "relating to their meaning in the various fields of medicine, being, however, a key to the available literature rather than a comprehensive or critical survey." Part Three addresses itself to the "Therapeutic Considerations and Concluding Remarks." A bibliographic list of 2251 references corresponding to the divisions of the text occupies 121 pages. In addition there are complete subject and name indices. The scope of the bibliography alone represents an achievement possible only through the organized efforts of a subsidized group; a task beyond the capacity of the individual, who cannot hope to keep abreast of the ever mounting volume of current literature related to the subject, and especially to have a knowledge of the literature from the foreign sources, of which in this book 50% are in German and 6% in other foreign languages.

One notes the beginning transition of medical thought from the mechanistic tradition to the *organismal* theory involving the new concept of the *organism-environment* equilibrium, the concept of the total personality in terms of health and disease. In the sense of Bleuler's dictum that "a physician who thinks in terms of psychogenesis will never become an agent in pathogenesis," this corpus of new thought should widen the perspective and understanding of the physician confined in practice to the single organ or organ system. This volume has much to offer the physician to the end that he no longer contribute to his patient's irremedial invalidism. The author wisely cautions against the overemphasis of psychotherapy in special practice: in the approach to these problems the exclusive emphasis of the psychic is as narrow as that which holds that every psychic disturbance is purely physical in origin. The profession is at the threshold of a new discipline in which there is room for both the conservative and the doctrinaire.

This book fulfills a twofold purpose: first, as an invaluable reference work for the specialists in the fields of psychiatry, neurology and of psychosomatic interrelationships, and second, as a treasury of stimulating information for the practitioner to whom the current literature pertaining to this subject is inaccessible. The book is especially recommended to the young physician. Dr. Dunbar and her collaborators deserve commendation for their prodigious and timely labors in contribution to one of the most vital and vexations of problems.

P. R.

NEW BOOKS.

- Clinical Laboratory Methods and Diagnosis.* A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories, Gradwohl School of Laboratory Technique, and Laboratories, St. Louis County Hospital, etc. Pp. 1028; 328 text illustrations and 24 color plates. St. Louis: The C. V. Mosby Company, 1935. Price, \$8.50. (Review, p. 275.)
- A *Bibliography of the Poem Syphilis Sive Morbus Gallicus*, by Giorolamo Fracastoro. By LEONA BAUMGARTNER, and JOHN F. FULTON. Pp. 157; 9 illustrations. New Haven: Yale University Press, 1935. Price, \$5.00.
- Maimonides (The Rambam).* The Story of his Life and Genius. Octo-centennial Edition. By Dr. J. MÜNZ. Translated from the German, with an Introduction, by HENRY T. SCHNITTKIND, PH.D. Pp. 238. Boston: Winchell-Thomas Company, 1935. Price, \$1.50. (Review, p. 271.)
- International Clinics. Vol. 2, Forty-fifth Series, 1935.* Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 327; many illustrations, some in colors. Philadelphia: J. B. Lippincott Company, 1935.
- The outstanding articles in this number offer survey (Prognosis in Heart Disease, Pneumonokoniosis, Headache, Anemia, Heart Pain, Pyuria in Childhood, etc.) rather than present original evidence.
- Indian Journal of Pediatrics, Vol. 2, No. 7 (April, 1935).* Edited by Dr. K. C. CHAUDHURI, with 11 Collaborators. Pp. 65; illustrated. Published quarterly in Calcutta. Price, Annual Subscription, Rs. 6/-; Single Number, Re. 1/8.
- An Outline of Immunity.* By W. W. C. TOPLEY, M.A., M.D., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology in the University of London. Pp. 415; 37 illustrations, 63 tables. Baltimore: William Wood & Co., 1933. Price, \$6.00.
- The Evaluation of Symptoms.* Offered after Fifty Years in Medicine. By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., Professor of Therapeutics, Emeritus, and formerly Clinical Professor of Medicine, Yale University. Pp. 163. New Haven: Yale University Press for the Author, 1935. Price, \$3.50. (Review, p. 276.)
- La Vie Médicale aux XVI^e, XVII^e et XVIII^e Siècles.* By DOCTEUR PAUL DELAUNAY, Membre de la Société Française D'Histoire de la Médecine. Pp. 556; 114 illustrations. Paris: Éditions Hippocrate, 1935. Price, 40 francs. (Review, p. 275.)
- Diet Control.* A System of Eleven Hundred Diets for the Prescription of Diabetic, Anti-obesity and Measured Diets in General. By GEORGE E. ANDERSON, M.D., Attending Physician to The Brooklyn and The Lutheran Hospitals; Chief of Metabolic Clinic, The Brooklyn Hospital, and PAUL CHADBOURNE ESCHWEILER, M.D., Assistant Attending Physician to The Brooklyn and The Methodist Episcopal Hospitals; Senior Physician, Metabolic Clinic, The Methodist Episcopal Hospital, New York: Gallo & Ackerman, Inc., 1935. Price, \$3.50.
- The Depopulation of Pacific Races.* Bernice P. Bishop Museum Special Publication 23. By S. M. LAMBERT. Pp. 42; 11 illustrations and 19 tables. Honolulu: Bishop Museum Press, 1934. Price, \$1.00.
- The Woman Asks the Doctor.* By EMIL NOVAK, M.D., F.A.C.S., HONORARY D.Sc. (DUBLIN); Associate in Gynecology, Johns Hopkins Medical School; Former Vice-President American Gynecological Society. Pp. 189. Baltimore: The Williams & Wilkins Company, 1935. Price, \$1.50.

- Some Thoughts of a Doctor.* By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A. With a Preface by SIR W. LANGDON BROWN, M.A., M.D., F.R.C.P., Regius Professor of Physic in the University of Cambridge. Pp. 183. London: H. K. Lewis & Co., Ltd., 1935. Price, 6s.
- The Problem of Mental Disorder.* A Study Undertaken by the Committee on Psychiatric Investigations, National Research Council. Members of the Committee: Madison Bentley, Chairman, Sage Professor of Psychology, Cornell University; E. V. Cowdry, Professor of Cytology, Washington University. Pp. 388. New York: McGraw-Hill Book Company, Inc., 1934. Price, \$4.00.
- The Proceedings of the Charaka Club, Vol. VIII.* Post Multa Virtus Opere Laxare Solet. Pp. 202; illustrated. New York: Columbia University Press for the Charaka Club, 1935. Price, \$5.00.
- The Spleen and Resistance.* By DAVID PERLA, M.D., Associated Pathologist and Bacteriologist, Montefiore Hospital, and JESSIE MARMARSTON, M.D., Associate in Pathology, Cornell University Medical College. With a Foreword by DAVID MARINE, M.D., Pp. 170. Baltimore: The Williams & Wilkins Company, 1935. Price, \$2.00.
- The Story of Medicine in the Middle Ages.* By DAVID RIESMAN, M.D., Sc.D., Professor of the History of Medicine and Professor Emeritus of Clinical Medicine, University of Pennsylvania; Member, History of Science and Medieval Academy of America. Pp. 402; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, \$5.00.
- Clinical Tuberculosis*, in two volumes. Edited by BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois College of Medicine, etc. With the Collaboration of 33 Contributors. Pp. 1580; illustrated with over 640 half-tone and line engravings and 9 full page color plates. Philadelphia: F. A. Davis Company, 1935. Price, \$22.00.
- Krebs im Licht Biologischer und Vergleichend Anatomischer Forschung.* By MED. DR. JOSEF LARTSCHNEIDER, LINZ A. D. DONAU. 11 Band, 2 Heft: Adenomkrebs Kystom Scirrhus Bindegewebe Mesenchym Sarcom Odontom Kieferkystom. Pp. 197; 57 illustrations. Wien: Franz Deutsche, 1935. Price, M. 7.

NEW EDITIONS.

- The Treatment of Rheumatism in General Practice.* By W. S. C. COPEMAN, M.A., M.B., B.CH. (CANTAB.), M.R.C.P. (LONDON), Hon. Physician, B.R.C.S., Clinic for Rheumatism, Peto Place; Assistant Physician, West London Hospital, Children's Department and Hospital of St. John and Elizabeth, etc. With a Foreword by SIR WILLIAM HALE-WHITE, K.B.E., M.D., F.R.C.P., Hon. LL.D., Consulting Physician to Guy's Hospital, etc. Pp. 228. Second Edition. Baltimore: William Wood & Co., 1935. Price, \$3.25. (Review, p. 273.)
- Manual of Dehydrated Culture Media and Reagents.* Pp. 198. Fifth Edition, revised. Detroit: Difco Laboratories, Inc. (Price not given.)
- The Treatment of Fractures.* By DR. LORENZ BÖHLER, Director of the Hospital for Accidents, Vienna; Lecturer on Surgery in the University of Vienna. Pp. 578; 1039 illustrations. Fourth English Edition, Translated from the Fourth Enlarged and Revised German Edition by ERNEST W. HEY GROVES, M.S., M.D., F.R.C.S., Consulting Surgeon, British General Hospital; Emeritus Professor of Surgery, University of Bristol, etc. Baltimore: William Wood & Co., 1935. Price, \$12.00. (Review, p. 276.)

PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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PILONIDAL SINUS.

HARDLY any condition in the field of minor surgery is so little understood either as to the exact nature or treatment as is that of pilonidal sinus. It has been the subject of many articles in the surgical literature of the past 10 years and it is commonly seen and recognized in every good surgical clinic. However, it is apparent that among general practitioners the condition is not commonly recognized or understood, since so frequently the surgeon sees the patient after the lesion has been repeatedly treated as a simple abscess and multiple incisions have been made to drain the contents.

The lesion is also called sacrococcygeal cyst, sacrococcygeal fistula, sacrococcygeal sinus and pilonidal sinus, the latter term having been given it by Hodges¹ because of the nest of hair so frequently found within the sinus. Anderson,² in 1847, reported a case of a 21-year-old man who had a "scrofulous sore" over the sacral region following a blow over the area 6 months previously. On examination there was a very small sinus, too small to admit a probe. There was an abscess present which was opened and later fine, soft hair was removed from the wound. J. Mason Warren³ reported 3 cases before the Boston Society for Medical Improvement in 1854. His description is so clear that it merits recording in this review: "Abscess, containing Hair, on the Nates—Dr. J. Mason Warren had met with three cases of abscess of the nates connected with a fistulous opening over the coccyx, containing hair. The last case is a type of the two others. The patient, a young man, 20 years old, had for some time suffered from an irritation on one of the nates. Finally, an abscess formed and broke, followed shortly by one on the opposite side, both being the sources of great discomfort, the first having become fistulous. On separating the nates, Dr. W. at once discovered, about an inch below, in the median line and over

the coccyx, a small aperture, about large enough to admit a probe, looking like a pit in the skin, and lined with epidermis. A probe, being introduced, penetrated to the depth of an inch and a half.

"From his experience in the two former cases, Dr. W. was at once able to say that it led to a cavity containing hair, which was probably the origin of the abscess in the neighbourhood. An incision being made into this canal, it was found to terminate in a suppurating cavity, in which, lying quite loose, was a small bundle of hair. Radiating from this cavity were two canals leading to the abscesses in the nates mentioned above.

"It would seem probable that originally the hair was contained in a cyst, which, from the irritation caused by sitting, had suppurated, and the pus had burrowed in different directions."

In 1880 when Hodges wrote his classical description and suggested the most popular name for this condition there had already been a number of cases reported in the literature, although the condition was not generally recognized even by surgeons. In 1892 Mallory⁴ reported 19 cases collected from the literature. That these cases did not represent the total number reported up to the time of publication is evident from the omission of the cases of Beall,⁵ Mason,⁶ Wendelstadt,⁷ and others, nor did Mallory regard his report as complete, as he stated that he "appended a limited number of cases" to illustrate the main points of his paper. We are led to assume that by 1892 the condition was moderately well recognized by surgeons generally. The consensus of opinion in regard to treatment was that the cyst should be laid open, the contents removed, and the cyst wall curetted or excised.

The early discussions of the etiology of pilonidal sinus, like those current today, accepted the congenital nature of the lesion. Hodges¹ felt that the condition was caused by loose hair lodging in the post-anal dimple but offered no explanation of this defect except that it was congenital. Warren explained the condition on the basis that a hair follicle in the sacrococcygeal region became reversed, the hair growing inwards and continuing to grow drew the hole in after it by invagination. Aside from these novel explanations the chief theories as to the formation of pilonidal sinus are (1) a failure of the two halves of the body to unite; (2) failure of the medullary canal to become obliterated over the sacrum; (3) invagination of ectodermal structures over the sacrum.

The statement that pilonidal sinuses are caused by the failure of the two halves of the body properly to unite is a general one and gives no detailed concept of the actual processes which are responsible. Since it is always found at or near the midline, this conclusion can be rather generally accepted if we agree that the condition arises on a developmental basis. This latter is quite universally accepted as true. Attempts to explain the nature of the aberration of development have been frequent. Mallory⁴ made microscopic sections in the sacral region of 7 fetuses ranging in age from $3\frac{1}{2}$ to 6 months and found a canal lined with epithelium in 6 which he interpreted as remnants of the neural canal. He felt that in these remnants of the neural canal lay the source of pilonidal sinuses. He was not alone in this belief at that time, as he quotes Hermann and Tourneux⁸ as holding the same view. Recently Weeder⁹ has adopted this theory. Lannelongue¹⁰ explains

the origin of the condition as due to the fact that the mesoblast is lacking particularly over the sacrum, the skin coming to lie close to the sacrum, and at places being bound to the bone. When subcutaneous tissue forms, these places where the skin is bound tightly to the sacrum forms dimpling, and if the depression is narrow enough may cause a sinus. A similar view was indicated by Stone¹¹ in his first paper on the subject. Later he indicated¹² that the condition was the result of a vestigial structure analogous to the preen gland in birds. A plausible explanation of the condition is that given by Oehlkecker,¹³ who pointed out that the caudal ligament attaches to a thin, hairless area of skin over the lowermost end of the spinal column. Due to discrepancies in rate of growth between skin and spinal column, shortening of the caudal ligament, and the growth of connective tissue between the skin and coccyx, the skin is drawn inwards and upwards, forming a dimple or even a sinus, depending on the amount of invagination present. Since the caudal ligament attaches to the so-called bald spot, the hair found in the sinus is the result of hair follicles in the region of the caudal bald spot which likewise has been invaginated. The formation of cysts is explained as being due to the usual metabolic products of the skin, which tend to block the opening, causing the inflammatory changes so frequently seen. Fox¹⁴ called attention to one discrepancy in Oehlkecker's theory in that if the so-called bald spot comes to lie over the sacrum instead of over the coccyx, the caudal ligament should cause the sinus to point downward from the skin over the sacrum toward the coccyx, instead of upward, as is the usual case. Fox, following a study of embryos, concluded that a pilonidal sinus originated following the invagination of ectoderm which is usually present in the fetus, and occasionally persists into adult life.

A clear, incontrovertible concept of the formation of pilonidal sinus is not as yet at hand. It is difficult to state definitely whether the condition is due to faulty development of the lower end of the medullary canal or to invagination of skin. The latter seems most plausible to us despite the rare reports of infection of the spinal sac from pilonidal sinus (Ripley and Thompson¹⁵ and Moise¹⁶), and the occurrence of cysts and sinuses of similar nature occurring anterior to the sacrum (Masson¹⁷ and Lahey and Eckerson¹⁸).

The frequent occurrence of postsacral dimple of the skin is an occurrence too common to be dismissed lightly and it is difficult to correlate these dimples of small or large size with medullary remnants. Markoe and Sehley¹⁹ report 89 dimples (29.1%) and 11 fistulæ (3.7%) in 300 consecutive births, while other figures given have ranged from 4% in adults to 39% in children. During physical examination made by one of us (C. G. J.) of 1040 men at a Citizens' Military Training Camp, 37 (3.6%) were found to have marked postsacral dimples or pilonidal sinuses. The majority of these individuals was under 21 years of age, and none was younger than 15.

Gross and histologic examination of sinuses removed at operation, even though infection has been present, likewise suggest that the sinus is of ectodermal origin. Descriptions of the examination of tissue removed has been reported by Newell²⁰ and by Fox.¹⁴ The sinus is usually a branching or arborescent cavity, and apparently because of previous inflammation the lining consists largely of granulation tissue.

Hair may or may not be found in the cavity, usually lying free, rarely it is attached to the wall at the site of a hair follicle. True skin is commonly found lining some portion of the canal, fully developed sweat glands and hair follicles being present.

The history that one obtains from patients who are found to have a pilonidal sinus is usually clear enough to make the diagnosis, and this in addition to the physical examination should make the diagnosis easy. The patient is usually of early adult age, and complains of a discharge from the end of the spine. Usually the patient definitely states that the discharge is not from, but above the rectum and is sufficient to stain the clothing only occasionally. Many patients give the history that after discharging for some time the discharge stopped and a sore swelling developed over the sacrum. Following incision or spontaneous discharge of pus the wound healed slowly, only at a later date to have the swelling and tenderness recur. This cycle is often repeated many times until the diagnosis of pilonidal sinus is made by someone familiar with the condition. On physical examination a small dimple may be noted just above the tip of the coccyx. This dimple may be small enough to be represented by a small pin-point area, or it may be 0.5 cm. in diameter. If the opening is large enough to admit a probe, the instrument will usually pass upwards and towards the sacrum. A small drop of white or purulent fluid may be found at the opening. This material is usually increased in amount if gentle pressure is made over the sacrum.

In those patients who have suffered the mass to be incised, or who have had abscess formation with spontaneous rupture, one or more thick, wide scars may be seen over the sacrum, usually at a distance from the opening or dimple over the coccyx. These scars may be seen high over the sacrum or even on the buttocks, but usually they are found to lie over the middle of the sacrum. The majority of the sinuses contain hair, and if they have undergone abscess formation and are found open, hair may be found in the wound. In some cases there is no evidence of hair present and there is no history of any having been found at any previous time.

Of the first cases reported by Warren, 2 were females and 1 male. However, when one looks over the case reports in modern literature the proportion of females to males is low. In a series of cases operated upon on our service at the Hospital of the University of Pennsylvania there were 44 males and only 9 females. The proportion of females to males in the cases reported by Cattell and Stoller,²¹ Glenn,²² Stone,¹¹ Rogers,²³ Ferguson,²⁴ Owen,²⁵ Giffin and Archibald²⁶ and Masson¹⁷ were about 1 to 4 (505 cases; 407 males and 98 females). In all these series there was a marked preponderance of males. Newell²⁰ has reported 11 cases all in females. It is possible that this preponderance of females may be accounted for by the source of Newell's clinical material. A distorted picture of the sex distribution of pilonidal sinus might be obtained should the cases be reported from a gynecologic clinic.

Newell's²⁰ cases ranged from 20 to 37 years of age. Most of the cases reported in the literature were found to be in early adult life. Our oldest case was 58 years old, the youngest 1½ years. It is to be remembered that age distribution of pilonidal sinus which comes to operation and those present but which are dormant are very likely

quite different. The surgeon seldom sees these cases unless infection has ensued, and usually does not see them until after the patient has had several incisions made by the general practitioner. In this regard Stone¹¹ and Ottenheimer²⁷ suggest the excision of symptomless and uninfamed pilonidal sinuses as a prophylactic measure. The difficulty in accepting this as a principle is that it is not only hard to determine which cases will have later trouble, but the identification of the condition is not easy until the sinus becomes dilated with its contents. A postsacral dimple in a child is hardly an indication that there is a sinus present. Nevertheless, should a sinus be found and well outlined there is little question but that it could be removed more safely and surely before inflammation has occurred than after.

The treatment of pilonidal sinus has varied from simple incision and curettage, as in the days of Warren, to radical excision as practised at the present time. For a time block excision of the sinus tract was the common method of treatment, in most cases the large defect resulting being packed open and allowed to granulate. This method requires prolonged dressing care and the end results are not always of the best. Lahey²⁸ called attention to the fact that the thick scar resulted in pain on sitting which caused considerable annoyance. Wide dissection of the sinus does not always give a good result, as even by this method of treatment recurrences occur. Lahey thought to replace the tissue removed from over the sacrum with a pad of fat drawn from over one buttock. The large defect would then lie over soft tissue and obviate the hard scar over the sacrum. This method of closure, while decreasing the scar over the sacrum, does not obviate the large defect which requires a long period of dressing.

The ideal method of treating pilonidal sinuses is that of complete excision of the tract after the injection of a suitable substance in the sinus to outline the tract, with primary closure. In order that an excision be successful the entire sinus tract must be removed. Small portions of the sinus left behind tend to cause a recurrence, and unless the sinus is well outlined it is quite easy to leave the remnants behind. In our own experience methylene blue to which hydrogen peroxid has been added as suggested by Stone¹¹ serves this purpose well. Melted paraffin may be used as suggested by Newell²⁰ for injection. The paraffin hardening tends to keep the sinus dilated during dissection, facilitating complete removal. If this method is used the injection must be made under enough pressure to insure complete filling, and the paraffin must not be allowed to cool before the small branches are reached.

We prefer, when possible, to dissect the sac out completely, with the sinus always under view and for this reason prefer not to resort to block excision. This method requires a little more time than block excision but there is no needless sacrifice of postsacral tissue.

When we are sure that the sinus is entirely removed, the wound is closed tightly. Silkworm gut stay sutures are placed in the depths of the wound on either side and brought out through the skin on the opposite side where they are tied over a gauze roll or lead wire to provide snug approximation and obliterate dead space. This method of closure is somewhat similar to that described by Colp,²⁹ except we have only occasionally had to resort to undermining of the skin flap

to obliterate dead space. The skin edges are approximated when necessary by silk or dermal sutures. In the depths of the wound only a minimum of catgut is used to control hemorrhage. In the majority of cases pressure applied over the bleeding points for a short time is sufficient to control all bleeding. We have had no difficulty with post-operative hemorrhage in the closed cases.

Following operation a snug dressing is applied and not disturbed for 5 days unless the patient's general reaction suggests trouble with the wound. The patient is kept in bed from 5 to 7 days.

For anesthesia we prefer spinal or local when possible. We do not feel that there is a tendency to spread infection by the use of local anesthesia since we attempt to infiltrate about and not through the operative site. We do not attempt operation on acutely inflamed sinuses but prefer to allow any redness or local heat to disappear before attempting removal.

Occasionally the sinus is too large to permit of primary closure throughout. Our policy is to treat these by partial closure with drainage. If none of the tissues about the area can be easily approximated the wound is packed open and the wound is allowed to granulate from the bottom. Rarely is it possible to suture these wounds secondarily.

Ferguson²⁴ advises the excision of pilonidal sinuses with primary closure. His results are excellent. We do not, however, feel that these patients should be permitted to get up after operation, as suggested by Ferguson. The wound should be allowed to heal before the patient is permitted ambulatory exercise. Not all wounds closed primarily will remain closed. The patient should be watched for infection in the wound, and when it is present the wound should be opened and packed. The treatment in this event is similar to that of a wound which is packed open primarily. Under this régime an attempt has been made to shorten the patient's convalescence and provide him with a wound which has the minimum of scar. If, however, the attempt at primary closure is not successful, the patient is no worse off than had the wound been packed primarily.

The treatment of pilonidal sinus which we have discussed is that of simple postsacral sinuses. This type forms the vast majority of those found; those penetrating the sacrum as described by Weeder⁹ are rare, as are those in which the sinus extends under the coccyx and lies anterior to the sacrum. Naturally, pilonidal sinuses found in these unusual locations require special treatment since they are not so easily accessible and require more extensive dissection.

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- (Titles have been omitted for sake of brevity.)

OPHTHALMOLOGY

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RECURRENT HEMORRHAGES INTO THE RETINA AND VITREOUS.

THE most characteristic cases of the syndrome of recurrent hemorrhages into the retina and vitreous are those occurring in young adults, usually males, between the ages of 18 and 30 (Eales' disease). Quite similar cases are seen at times in older patients, which should probably be taken into consideration in a general discussion of the nature of the process.

The clinical course and ophthalmoscopic appearances of cases of this type are generally well recognized, and the major interest has centered in the study of the etiology and management of the disease. Clinically, the characteristic feature is the occurrence of repeated attacks of blurring of vision due to more or less massive hemorrhages into the retina and usually simultaneously into the vitreous of one or both eyes. Ophthalmoscopically, at the onset of an attack it is often impossible to see the details of the retina because of the clouding of the vitreous

by the hemorrhagic extravasation. In the interim between attacks, after the vitreous has cleared, which it usually does more or less spontaneously at least in early episodes, it is possible to see that the source of the bleeding is a lesion of one or more of the retinal veins. This lesion usually is characterized by a localized perivenous infiltration, often associated with marked irregularity in caliber and localized dilations of the veins, and at times with obliteration of small venous branches later followed by the proliferation of new vessels into the retina and vitreous (retinitis proliferans). At times, foci of choroidal inflammation are seen, usually in the stage of atrophy and scarring; but it is doubtful if these can be considered to be the source of the hemorrhage. Damage to the arterial walls is also visible at times; but again the arterial lesions are probably of secondary origin. It seems most likely that a disease of the walls of the retinal veins is the primary lesion in all cases of recurrent hemorrhages into the retina and vitreous (Leber¹). The outcome of many of these cases is more favorable than would be thought possible from the ophthalmoscopic appearances in the active phases of the disease. Some, however, terminate in detachment of the retina as the end result of the proliferation of vessels and scar tissue in the retina and vitreous, and in some the blood clots in the vitreous are never satisfactorily absorbed.

The etiology of these cases has remained rather obscure, even up to the present time. Numerous rather vague causes were assigned by most of the earlier authors: constipation, vicarious epistaxis, hemophilia, oxaluria, phosphaturia, gout, hyperthyroidism and other endocrine disturbances. Zentmayer² particularly favors some adrenal dysfunction as the underlying factor. Since it was first suggested by Noll³ in 1908 that tuberculous lesions of the retinal veins were responsible, the belief in the probable tuberculous etiology of recurrent hemorrhages into the retina and vitreous has grown rapidly in favor. In 1921, Finnoff⁴ listed 108 reported cases. In this series, the etiology given was syphilis, 5; constipation, 8; focal infection, 4; menstrual disturbances, 2; disturbances of the blood and circulation, 3; tuberculosis, 35, and cause undetermined, 51. Of the 5 cases reported by Finnoff himself, 3 were thought to be due to tuberculosis and 2 to focal infection.

In 1929, Young⁵ reported 3 cases of recurrent hemorrhages into the retina and vitreous. One patient also had pulmonary tuberculosis. In the other 2 a low blood calcium was found: 6.5 mg. per 100 cc. in the first case and 9.5 mg. per 100 cc. in the second case. Calcium therapy apparently controlled the hemorrhages in the first case. Young analyzed the etiology of the cases reported up to the date of his paper. He found the causes listed as gastro-intestinal in 9, syphilis in 6, menstrual disturbance in 3, hyperthyroidism, hypertension and renal insufficiency in 4, focal infection in 10, tuberculosis in 76, and undetermined in 68.

Because of the fact that the syndrome of recurrent hemorrhage into the retina and vitreous is only rarely seen in association with clinical tuberculosis in other parts of the body, the diagnosis of tuberculosis in these cases must rest essentially on the patient's sensitivity to tuberculin. By some oculists the presence of a positive skin reaction to tuberculin is considered to be sufficient proof of the tuberculous nature of the ocular lesion. Most clinicians are not willing to accept such a

reaction as positive proof. Finnoff believed that the occurrence of a focal reaction in the eye after administration of tuberculin was necessary to establish the tuberculous etiology. It is rather dangerous in many of these cases to run the risk of a focal reaction in the eye, so that the diagnosis of tuberculous periphlebitis as the source of the hemorrhages is often difficult to establish, except presumptively.

Histologic examinations are seldom obtained in cases of this type, so that the actual anatomic nature of the local lesions has been difficult to demonstrate. In 1914, Fleischer⁶ reported the histologic examination of a case of recurrent hemorrhages into the vitreous in which the eye was removed because of secondary glaucoma. He found a widespread tuberculous periphlebitis and endophlebitis of the retinal veins, characterized by a proliferation of endothelial cells and giant cells. Tubercle bacilli could not be found. It should be noted that the patient in this case had pulmonary tuberculosis.

In more recent years, the causative influence of focal infections in these cases of recurrent hemorrhages into the vitreous has received considerable support. This etiologic diagnosis lacks positive proof, since it must be based simply on the apparent response to the removal of foci of infection. Benedict⁷ was unwilling to accept the focal infective origin in his cases since he could not reproduce the disease in rabbits by the injection of streptococci isolated from the foci of infection. In 1927, Godwin⁸ reported a case which showed no response to tuberculin therapy but which cleared up after a radical operation on the frontal sinus. In 1934, Swab⁹ reported 5 cases. He considered 3 of these to be due to tuberculosis and 2 to streptococcal focal infection. One of his cases had had pulmonary tuberculosis. In 1, the diagnosis of tuberculosis was based on the occurrence of focal reactions in the eye on the administration of tuberculin. In the third case considered to be tuberculous, the Mantoux test was positive and the disease responded favorably to the administration of tuberculin after the removal of foci and autogenous vaccine therapy had failed to influence its course. In 1 of these cases, the source of the hemorrhages was apparently an arterial instead of the usual venous lesion. The 2 cases considered to be of streptococcal origin responded favorably to the removal of infected teeth and the administration of autogenous vaccine. Tuberculin tests were negative in these 2 cases. Swab thinks that retinitis proliferans is a frequent sequel in the tuberculous cases but not in the ones associated with focal infection.

Recurrent hemorrhages into the vitreous occur in a certain number of patients with diabetes mellitus. The localized lesions in the retinal veins which are the source of the hemorrhages are quite similar to, if not identical with, those seen in the recurrent hemorrhages of adolescents (Eales' disease), and *retinitis proliferans* is an almost constant sequel. The patients are older than most patients with recurrent hemorrhages of tuberculous or focal infective origin, but usually younger than those with the more ordinary types of diabetic retinitis. In the series of 1052 cases of diabetes recently reported by Wagener, Wilder and Dry,¹⁰ recurrent hemorrhages into the retina and vitreous with retinitis proliferans occurred in 19 cases. Waite reports 31 cases of hemorrhage of this type associated with lesions of the veins among

2002 diabetics. He believes that "this group is derived from diabetic patients with cardiovascular-renal complications and with outspoken disease of the retinal vascular tree. The part played by diabetes alone in this group seems to be trivial." It seems probable that in these cases the possibility of a local retinal tuberculosis complicating the diabetes is at least worthy of consideration.

The treatment of these recurrent hemorrhages into the vitreous has always been rather unsatisfactory. Some cases progress to an unfavorable termination in spite of treatment; others do surprisingly well without treatment. Unquestioned healed lesions of the veins of the characteristic retinitis proliferans type are seen at times in patients who have been unaware of any previous trouble with the eyes. Consequently, it is often difficult to evaluate properly the effects of any particular treatment. Essentially, two lines of therapy are possible: first, direct treatment of the cause and, second, treatment directed toward the absorption of blood in the vitreous without reference to its systemic etiology. If the etiology of the disease can be fairly definitely determined, specific treatment can be used. Thus Finnoff,⁴ Wilmer,¹¹ Knapp,¹² Swab⁹ and others recommend the administration of tuberculin in the tuberculous cases. Proven syphilitic cases should, of course, be appropriately treated. Foci of infection should be removed, if present, and Swab recommends the administration of autogenous vaccine in these cases. In cases of undetermined etiology, calcium therapy, injections of whole blood and of gelatin and various other measures have been suggested for the control of the bleeding.

In the cases of proven or suspected tuberculous origin, some authors believe that tuberculin therapy is dangerous because of the risk of focal reactions in the eye with increased hemorrhages. They prefer, therefore, a non-specific type of treatment in these as well as in the cases of undetermined origin. This form of treatment is directed particularly toward the absorption of the blood in the retina and vitreous, and to the building up of the patient's general resistance as an aid to the always-present tendency to spontaneous healing of the local lesions in the veins. Potassium iodid was the earliest favored drug, but its effect on tuberculous lesions is questionable if not definitely harmful. In the discussion of Finnoff's paper in 1921, Benedict reported favorable results from the non-specific use of arsphenamin. More recently, at The Mayo Clinic, intravenous injections of gold sodium thiosulphate have been used with even more favorable results. As with arsphenamin, gold sodium thiosulphate was tried in cases of probable retinal tuberculosis because of its beneficial effect on tuberculous lesions of the skin. Whether it has a more specific action on tuberculous than on streptococcal phlebitis is difficult to say at the present time.

As noted by Waite,¹³ the prognosis in the cases of recurrent hemorrhages into vitreous in diabetes is uniformly poor. No form of treatment has been seen to give satisfactory results. Almost all of these cases end ultimately in blindness from retinal detachment or from organization of the blood in the vitreous. I have seen one patient, however, who recovered apparently spontaneously without diabetic or other form of treatment.

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ORIGINAL ARTICLES.

THE DIAGNOSIS OF PERIARTERITIS NODOSA.

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ALTHOUGH Rokitsansky¹ is properly credited with the first pathologic description of periarteritis nodosa, he apparently had no appreciation of the clinical implications of his observations at necropsy. In 1866 Kussmaul and Maier² first correlated the clinical and the pathologic findings in this condition and gave it the generally accepted designation, periarteritis nodosa. Since that time over 200 cases have been reported in the literature, but the intra-vitam diagnosis is still unusual. From the accumulated knowledge of the pathologic sequences of this affection and its resultant clinical pictures it has seemed that a more orderly approach to the problem should render its recognition in life more ready.

The primary lesions are in the small arteries and arterioles, the larger elastic arteries and veins escaping. The general pattern is of an acute inflammation of the vessel wall, loss of muscle, repair and proliferation. Probably the inflammatory agent enters from the adventitial side of the vessel wall, being transmitted by the periarterial lymphatics.³ There ensue degeneration of the muscle fibers of the media and coagulative and hyalin necrosis which may spread to the intima. A fibrinous and acute cellular exudate soon invades all layers of the arterial wall. This process is followed by a dense infiltration with lymphocytes, plasma cells and eosinophils. Injury of the intima leads to thrombosis. Medial injury and dila-

tation result in the formation of aneurysms. Frequently these aneurysms rupture and may thereby induce fatal hemorrhage. The acute exudative stage is succeeded by a fibroblastic proliferation in all coats with marked intimal thickening and a reduction of the lumen, replacement of the medial muscle and perivascular scarring. Canalization of thrombi may take place; and the organization of thrombosed aneurysms gives rise to firm periarterial nodules. During this reparative proliferation there remains a somewhat thinned infiltration of lymphocytes, plasma cells and eosinophils. In many of the reported cases there have been no gross periarterial nodules, and the pathologic diagnoses have not been reached until the microscopic examination. In these cases the arterial walls appear to have been strengthened promptly by reparative processes thus preventing aneurysm formation.

Many patients die in the acute phase of the disease, and in these cases the earlier lesions described would predominate. Other cases survive for a longer period, and in them the reparative processes are the most marked. The arterial lesions are not usually general, but affect widespread groups of vessels. These lesions cause infarction, degeneration, atrophy and scarring in the areas supplied. Gangrene is common if the hollow viscera are affected. The symptoms, signs and progress of cases probably depend as much upon the secondary reduction of blood supply to the various organs as they do on the primary arterial affection.

In 1928, Strong,⁴ from his review of the literature, gave the following order of frequency of involvement of the arteries: 1, Renal; 2, coronary; 3, mesenteric; 4, hepatic; 5, arteries to other viscera; 6, cranial; 7, peripheral. The kidneys are commonly contracted and show much vascular scarring and infarction. When the coronary vessels are affected, the myocardium may show considerable patchy fibrosis. Gangrenous enteritis occurs secondary to mesenteric artery involvement. Probably peripheral artery lesions should rank higher in the above list, but specimens are not usually taken in routine autopsies. The organs least commonly involved are the brain and lungs.

From this brief discussion of the pathology of periarteritis nodosa, it may be inferred that the clinical manifestations of the disease may be extremely diversified. Indeed, it has been mistaken for "trichinosis, Werlhof's disease, typhoid fever, miliary tuberculosis, polymyositis, arteriosclerosis with sclerosis of the kidneys, neuritis multiplex, gastro-enteritis, pyemia, hemorrhagic nephritis, serositis tuberculosa, influenza with renal hemorrhage, purpura hemorrhagica," according to von Haun.⁵ Harbitz⁶ differentiated the gastro-intestinal, renal, neuromuscular, cardiac, cerebral and cutaneous forms of periarteritis.

In the interest of clarity it has seemed much more logical to focus attention upon points of clinical similarity rather than to pursue

the diffusive course of possible differential diagnosis. To this end the suggestion of Meyer⁷ is particularly helpful. He pointed out that from among the multiplicity of manifestations, the following were the most conspicuous: "Chlorotic marasmus, polyneuritic and polymyositic symptoms; abdominal symptoms (sense of pressure, bloody diarrhea, vomiting, finally perforation and peritonitis). There is also often rapid pulse and albuminuria." To these dominant manifestations Brinkman⁸ added nephritis. Almost without exception the reported cases have shown varying manifestations of obscure sepsis. Yet it does not seem logical to divide the clinical tableau, as have Hutinel and his fellows,⁹ into infectious, digestive and cutaneous syndromes. The recent report of Curtis and Coffey¹⁰ offers a sound approach to the diagnostic problem presented by periarteritis nodosa in the analysis of the clinical data after the numerical method of Louis. Unfortunately this review involves only 38 cases as reported in the English language. Of the important data established, the following may be cited: 40% had a febrile course; a like proportion had neuritis and abdominal pain; 24% showed edema; weakness was conspicuous in 21%; and muscular atrophy was noted in 20%. The other clinical manifestations were scattered and did not suggest a specificity.

Much more ambitious was Arkin's attempt¹¹ to fit the clinical pictures into the four arbitrary pathologic stages which he listed as alterative—degenerative, acute inflammatory, granulation, and healed end stage or scarring. Since the earliest stage is purely microscopic, no characteristic clinical picture is suggested. In the acute inflammatory phase, constitutional symptoms of fever, chills and leukocytosis may be anticipated. Eosinophilia may also occur in the circulating blood. The localizing symptoms and signs depend upon the seat of the major pathologic involvement, *viz.*, gastrointestinal tract, peripheral nerves, heart, kidney and subcutaneous tissue. In the next stage of granulation, wherein healing and thrombosis may lead to vascular occlusion, anemia and cachexia predominate the constitutional picture; but more serious symptoms of renal insufficiency, cardiac failure, abdominal pain, gastro-intestinal ulceration and gangrene, peripheral neuritis, muscular atrophy and disturbances in the endocrine system may develop. With the cicatricial fourth phase, the last named sequences may be progressive, and Arkin subscribes to the diagnostic triad of Meyer as supplemented by Brinkman.

The routine laboratory studies in periarteritis nodosa are not conclusive. Curtis and Coffey¹⁰ relate the occurrence of leukocytosis in 32% of their surveyed group. Eosinophilia occurred in 12% of these 38 cases; but the occasional extremely high levels are more significant. In Curtis and Coffey's case a peak of 77% eosinophils in 19,900 leukocytes was observed. Lamb¹² found 51% eosinophils of a total white count of 20,900 in 1 of his 2 reported cases. The

eosinophils in Strong's⁴ patient reached the high level of 79% of 32,000. Schottstaedt¹³ reported 32% eosinophils of a total of 15,600 white cells; and Haining and Kimball¹⁴ 33% of 16,700. Taylor and Farley¹⁵ found 72% eosinophils in 25,700 leukocytes. These figures do not exhaust the available information upon this detail, but they suffice to emphasize the importance of the differential blood picture in this disease. It is significant that eosinophilia in the peripheral blood is by no means a constant finding. However, its occurrence must take on an added importance in the diagnosis and the differential diagnosis of periarteritis nodosa.

From a knowledge of the basic pathologic changes, evidences of renal involvement may be anticipated in a certain percentage of patients suffering from this condition; but in this connection it should be stated that there has long been recognized a marked discrepancy in the clinical expression of the disease as compared with the extent and degree of the vascular changes in the several organs. Albumin, casts and red blood cells may be expected in the urine of such subjects in varying quantities from time to time. With ultimate renal insufficiency the retention of protein end-products and the failure of dye elimination may constitute further marks of the vascular encroachment.

The eye grounds should theoretically afford an unusually fertile field of exploration for such vascular changes as occur in periarteritis nodosa. As a matter of fact, this promise is not fulfilled in actual study. Gruber¹⁶ maintains that there occurs only a neuroretinitis albuminurica secondary to renal involvement. Goldstein and Wexler¹⁷ studied the eye of a patient dying from periarteritis nodosa, in which no abnormality had been observed on a single antemortem ophthalmoscopic inspection, and found lymphocytic, monocytic and plasma cell infiltration about the choroidal vessels indicating a more chronic process than was evident in the visceral bloodvessels. They concluded that ophthalmoscopy should reveal scattered whitish foci which might even be mistaken for miliary tubercles. Singularly, no such findings have been reported in the literature. Strong⁴ reports puffiness of the eyelids, blurred optic disks and peripapillary edema. One of Goldstein's¹⁸ patients suffered ablatio retinae and scleritis. Taylor and Farley¹⁵ report diplopia, elevation of the optic nerve heads and retinal hemorrhages in their case. Pallor and white exudate in the retina appeared in Wever and Perry's patient.¹⁹

The intra-vitam diagnosis of periarteritis nodosa has been reported in 31 instances,* in several of which there apparently existed some reasonable doubt prior to the necropsy. It may profit to investigate the grounds upon which these clinical diagnoses were made. First, there may be grouped those 14 cases diagnosed from

* The case of Morowitz cited by Gruber is not included, since the reference is not accessible. The diagnosis was apparently made upon the biopsy of a nodule.

their clinical aspect and course. The second case of Kussmaul and Maier² was diagnosed by its similarity to their earlier one, and this diagnosis was confirmed by the characteristic appearance of the arteries in a biopsy of voluntary muscle. Kopp²⁰ recognized the clinical picture in his patient through the tetrad of Meyer and Brinkman. Biopsy of a subcutaneous nodule clinched the clinical impression. Both of Goldstein's¹⁸ cases were diagnosed by their characteristic course and findings. In one the typical vascular changes were later revealed in the arteries of an amputated leg, while in the second a biopsy of the subcutaneous nodules was confirmatory. In the case of Hutinel, Coste and Arnaudet⁹ the course was suggestive and a biopsy of the skin fixed the diagnosis. The conclusion of periarteritis nodosa was reached without the support of a biopsy in the cases of Sacki,²¹ Bansi,²² Gohrbandt,²³ Silbermann,²⁴ Carr,²⁵ Herrman,²⁶ and Stepp.²⁷ In the case reported by Rothstein and Welt,²⁸ a biopsy of the voluntary muscle failed to confirm the diagnosis, but the necropsy evidence was conclusive. Serious doubt is expressed in the diagnosis of von Spindler's²⁹ case, in that neither adequate clinical evidence nor histologic support is offered for the conclusion of periarteritis nodosa. Necropsy evidence has been offered in the other instances of an intra-vitam diagnosis without biopsy support.

The larger group of intra-vitam diagnoses of this unusual condition (17 cases) have been incidental to the more exhaustive study of obscure illnesses by biopsy. In a considerable proportion of this series both the biopsy investigation and the revelation of the vascular origin of the ailment have been candidly attributed to chance. As would be anticipated, the subcutaneous nodules have offered the most common point of attack for this diagnostic approach (9 cases). Schmorl,³⁰ Benedict,³¹ von Haun,⁵ Weigeldt,³² van Paassen,³³ Macaigne and Nicaud,³⁴ Lindberg,³⁵ Schottstaedt,¹³ and Grill³⁶ have recorded cases of periarteritis nodosa in which the intra-vitam diagnosis was rendered possible through the biopsy of accessible subcutaneous nodules. Since Kussmaul and Maier first determined the diagnostic availability of the biopsy of the voluntary muscles, one would anticipate its wider utilization than in the 2 reported instances of Carling and Braxton Hicks³⁷ and of Taylor and Farley.¹⁵ In the former a "lumpiness" was observed in the sural muscles and a biopsy revealed the existence of periarteritis nodosa, while in the latter a suspicion of trichinosis lead to a biopsy of the muscle.

The approach in the remaining scattered group of 6 cases of periarteritis nodosa in which the diagnosis was made upon the tissues removed during an operative procedure, may even more clearly be defined as intra-vitam recognition by chance. Manges and Baehr³⁸ report an instance in which the surgeon (Bucger) recognized the vascular lesions during an exploratory operation.

The diagnosis was confirmed by a biopsy of the mesentery. Gruber³⁹ diagnosed this condition from the histologic study of the gall bladder removed surgically. Friedberg and Gross⁴⁰ and Druss and Maybaum⁴¹ have placed on record instances of periarteritis nodosa recognized by biopsy of the appendix. Much more bizarre are the circumstances under which the diagnosis was made in the cases of Keegan⁴² and Gagstetter.⁴³ In the former a vague history of sepsis and right renal localization led to a nephrectomy. The excised kidney was studded with tiny white nodules grossly resembling miliary tubercles, but to microscopy showing "an acute and sub-acute obliterating arteritis limited to the arcuate arteries." Gagstetter's patient showed the characteristic lesions in the vas deferens, which was removed subsequent to a prostatectomy.

Renewed interest in the diagnosis of this unusual condition was aroused by the following patient:

Case History. CASE 1.—H. T., aged 48, a farmer, was first admitted to the Wisconsin General Hospital on December 2, 1934, with the chief complaint of "pain in the stomach," which the patient dated to October 1, 1934. At that time attacks of sour stomach and gaseous distention occurred after meals. The actual discomfort persisted from one meal to the next and there was no apparent relation to the type of food taken, except that sour foods seemed to aggravate the condition. After an initial period of 2 weeks' discomfort, there was a season of freedom from these symptoms until about November 15, 1934, when they recurred in the same order and were accompanied by pain in the epigastrium. This pain, which radiated about the costal margin and to the right groin, occurred immediately upon the taking of food and was absent when the stomach was empty. It had become progressively worse. The appetite was poor; flatulence was marked; nausea without vomiting was experienced. Diarrhea succeeded the medication prescribed by his physician. The stools were tarry on November 30, and on December 1 he passed a small amount of red blood in the stools. A cholecystotomy had been performed in 1931 for somewhat similar symptoms and the only relief experienced by the patient was a freedom from the biliousness that occurred before the operation.

The inventory by systems added the occurrence of steady frontal headache over the past 2 weeks accompanied by vertigo and respiratory difficulty, which had abated with the onset of the gastro-intestinal complaints. During the so-called asthmatic attacks, the patient expectorated as much as a pint of yellowish sputum per day. A backache had been remarked concurrently with the epigastric pain and there were frequent muscle spasms in the legs. The feet had been cold and there had been a steady, dull ache in the feet since the time of the operation. Paresthesias, especially numbness, were noted in the fingers about a week ago. A weight loss of 15 pounds from an average weight of 160 pounds had occurred in the last 2 or 3 weeks. The past medical history is significant in the incidence of the common childhood diseases; measles, mumps, chicken pox and whooping cough. Tonsillitis had also occurred. Cholecystotomy was performed in June, 1931, and some nasal operation for the relief of asthma in 1930. The social history was irrelevant except for the fact that the patient was a farmer. Family history revealed Bright's disease as the cause of death in the father.

Physical Examination. The patient was poorly nourished and showed evidence of recent weight loss. The weakness was apparent. The feet were cold, while the skin of the body was warm and dry. Tenderness was elicited

over both antra. Parenthetically, the patient stated that while driving to the hospital he had developed a sudden coldness and numbness of the left hand, a sharp pain on the ulnar side of the left hand and in the fourth and fifth fingers, radiating up the ulnar side of the forearm and arm to the shoulder and anterior surface of the left chest. The fundal vessels showed slight thickening. The chest was emphysematous in shape and showed some possible accentuation of the normal apical differences in vibratory phenomena. The percussion note was hyperresonant and the breath sounds somewhat diminished over the entire chest. The cardiac apex was to the right of the sternum in the fifth interspace 7 cm. to right of midsternum, and the cardiac dullness was mapped entirely to the right of the sternum. The mitral sounds were heard entirely to the right of the sternum; the aortic second sound was louder than the pulmonic second. The pulse rate was 84; the peripheral vessels were slightly thickened, and the blood pressure was 122/88. The liver edge was palpable at the left costal margin; the splenic edge was palpable at the right costal margin. Exquisite tenderness was elicited in the epigastrium, especially at the site of the postoperative scar; some tenderness was elicited in the left lower quadrant. There was some inability to adduct and abduct the fingers; he was unable to extend completely the fourth and fifth fingers, adduct the thumb, oppose, abduct or adduct the little finger on the left. An anesthesia was determined over the ulnar side of the left hand on the palmar and volar surfaces and of the fourth and fifth fingers except at the extreme tip of the fourth; there was hypesthesia of the ulnar surfaces of the forearm and the inner surface of the left upper arm and the anterior surface of the chest on this side. The deep tendon reflexes were present and active except for the patellar and Achilles reflexes, which were questionably absent. No paradoxical reflexes were determined at this time.

Laboratory Studies. Urinalysis showed albumin and occasional hyalin and granular casts; hemoglobin, 70%; color index, 0.7; erythrocytes, 4,600,000; leukocytes, 25,100; neutrophils, 51%; eosinophils, 40%, and small lymphocytes, 9%. A gastric analysis 3 days later showed 33 degrees total acid and 13 degrees free acid. Stools showed no ova or parasites. The blood Wassermann test was negative on 2 occasions, the spinal fluid Wassermann once. The gold sol curve was 0121100000, the Ross-Jones and Noguchi reactions were faintly positive, and no cells were found in the spinal fluid. The blood chemistry showed 105 mg. % sugar and 36 mg. % non-protein nitrogen. Repeated examination of the stool grossly and chemically showed no blood. A phenolsulphonephthalein dye output of 80% in 2 hours was noted. The 24-hour specimen of the urine showed no arsenic. The analyses of the hair and nails for arsenic showed normal values. The catheterized specimens of urine from the ureters showed a few pus cells and red blood cells from the left side and many red blood cells from the right. The cultures of these specimens were sterile. Detailed sensitization tests were done for the ordinary pollens, epidermals and foodstuffs without establishing a positive reaction in a single instance. An oral cholecystogram the day after admission showed no positive shadows; and although the shadow of the gall bladder was faint, there was no evidence of functional abnormality. The barium enema showed a complete transposition of the colon, the cecum being in the left lower quadrant, and there was some redundancy without obstructive lesions in the colon. The roentgenograms confirmed the fluoroscopic findings and established the transposition of the abdominal viscera. There was no intrinsic lesion determined. A gastro-intestinal series showed a situs transversus with the pylorus and duodenum on the left side, but there was no suggestive intrinsic defect in the upper gastro-intestinal tract. The Roentgen rays of the chest showed the heart in dextro-position. There was very slight haze at the

right apex without granularity. The hilum shadows were somewhat increased in extent and on the left side there were several large caseo-calcareous nodes. There were several calcific shadows along the left cardiac border. The peribronchial markings were accentuated throughout the lung fields. The diaphragms were rounded and smooth, and the sulci clear. The Roentgen ray of the sinus showed mucoperiosteal thickening in the left antrum and similar but less marked changes in the right antrum. Both ethmoidal areas were diffusely clouded. The frontal cells were extensive and deep but apparently clear. Bilateral pyelo-ureterograms showed partial duplication in the right and the left pelvis showed moderate dilatation. The orthodiagram confirmed the physical finding of a dextrocardia and showed a frontal area of 25% in excess of the predicted, and a transverse diameter 5% in excess of prediction. There was some lengthening of the left auricular salient. The electrocardiograms were taken 2 days after admittance and then after a period of a few more weeks and agreed in the details of normal rhythm, downward *Q-R-S* complexes in all leads, inverted *P*₁, *Q-R-S*₂ deeply notched, *Q-R-S*₃ notched at the base of downstroke and slightly slurred on upstroke, *ST* segment slightly elevated in Lead I, *T*₁ and *T*₂ flat. The auricular and ventricular rates were 85. The auriculo-ventricular conduction time was 0.14 second and intraventricular conduction time was 0.09 second.

Course. There was a slight febrile rise from the 7th to the 17th day. The temperature never exceeded 101° F. The pulse remained proportional to the temperature elevation, as did the respirations as a rule. After the subsidence of the slight febrile reaction, the pulse remained disproportionately high (84 to 104), even though the temperature went above 100° F. on only 2 occasions in the 29 days of his hospital stay. Proctoscopic examination the day after admission revealed no significant pathologic changes. Washings of the antrum were relatively free of infection. Repeated neurologic examinations revealed the cranial nerves intact. The changes in the left hand and arm persisted. Sensation in all expressions over the hands and feet was reduced and there was slight hypesthesia over the left anterior chest. The knee jerks were established only on reinforcement. There was an absence of the ankle jerks and the radial reflexes. The patient continued to complain of tiring of the jaws upon eating, and dated this back for a period of 10 weeks. Upon occasions the upper abdominal discomfort was relieved by the administration of atropin. This pain recurred and the abdomen was exquisitely tender from time to time. Active peristalsis was heard and there was no vomiting. It was interesting that the leukocyte counts ranged from 12,450 with 33% eosinophils to 32,950 with 72% eosinophils. The lowest eosinophil count on this admission was 0.7% of 21,350 leukocytes on the 9th day. Two days before discharge, or on the 27th day of hospitalization, the count was 60% hemoglobin, 4,360,000 erythrocytes, 16,350 leukocytes, 50% neutrophils, 40% eosinophils and 10% lymphocytes.

The impression of a partial intestinal obstruction was held at this time; but no satisfactory explanation was offered for the persistent eosinophilia. The patient was discharged on the 29th day with an impression of post-operative intestinal adhesions and situs transversus completus, duplication of the left renal pelvis, and idiopathic eosinophilia.

After 18 days at home he was readmitted (January 18, 1935) in a very markedly debilitated condition, with the statement that he was unable to evacuate his bowels. He belched gas continuously, experienced a feeling of fullness, and was unable to drink more than $\frac{1}{2}$ glass of water without nausea. Two days before admission he had vomited a greenish material, but there had been no vomiting before or since that time. Dull to sharp pain occurred in the right upper quadrant whenever fluids were taken.

A week previously the ankles had become very edematous and he was conscious of some fever. Cramps in the legs were noted.

The examination added little to the previous study except from a neurologic standpoint. The patient had obviously lost much ground. The neurologic examination showed no ataxia in the usual test movements. The biceps and triceps reflexes were markedly reduced, as were the right abdominal reflexes. The patellar and Achilles reflexes were reduced. The general muscle tone was very poor. Roughly symmetrical patchy disturbances of tactile and temperature senses were detected in both extremities. It became apparent that there was a bilateral peripheral involvement affecting the muscles of the hands, the right more than the left. The changes in the ulnar distribution were more marked. The right median nerve distribution was more markedly involved than the left. The bilateral involvement from the knees distally with paralysis of the muscles innervated by the peroneal and tibial nerves together with the changes in the reflexes in the arms indicated a rather extensive peripheral neuritic involvement. The peripheral edema became more marked and chemosis of the conjunctivæ was noted. Stupor supervened, acetone appeared on the breath, and the patient succumbed after a second period of 17 days' hospitalization.

In this period of hospital stay several added factors were gathered from laboratory study. Urinalyses regularly showed albumin and many granular casts. White blood cells were apparent from time to time. No Bence-Jones protein was found. The hemoglobin fell as low as 50% and the red blood cells to 3,570,000. The white blood cells ranged from 13,700 to 24,250. The neutrophils predominated and ranged from 62 to 94%, and only on 1 occasion, with the leukocytes at a level of 13,700, was there an eosinophilia (11%). The sputum was negative for tubercle bacilli. The blood glucose on this admittance was 75 mg. % and the non-protein nitrogen 52 mg. %. These figures were sharply altered, advancing steadily to 148 mg. % glucose and 86 mg. % non-protein nitrogen. The creatinin ranged from 1.6 to 1.9 mg. %. The blood chlorids were 345.8 mg. %. The total output of phenolsulphoneplthalein dropped to 25% in 2 hours. The total serum proteins were 5.2 and 6 gm. %, but the serum globulin equalled the albumin of 2.6 on the first occasion and then exceeded the serum albumin 3.2 gm. as compared with 2.8 gm. The sugar tolerance test done on the 14th day (3 days before death) showed a normal initial level of 80 mg., but the subsequent curve was quite unusual in that at the end of 1 hour a figure of 150 mg. % was established; 2 hours, 141 mg., and 3 hours, 144 mg. This was interpreted as an unusual diabetic curve. On this second admittance the pulse remained irregularly high; but the temperature never exceeded normal level and as a rule was subnormal.

When this patient was seen in consultation (5th day of second admittance) the clinical course, fever, polyneuritis, polymyositis, epigastric pain and eosinophilia led to the diagnosis of periarteritis nodosa. The subsequently advancing evidences of renal insufficiency seemed to clinch this conclusion, and added to these signs of widespread vascular encroachment came the significant sugar tolerance curve. In the absence of the typical subcutaneous nodules, a biopsy of the gastrocnemius muscle was made 6 days before death. No characteristic lesions were determined in these sections.

Autopsy (February 4, 1935; Dr. J. C. McCarter; 3 hours after death). The body is that of a well developed, poorly nourished white male about 40. An old healed upper right reectus incision which admits of some herniation is present. Well marked muscular atrophy of both legs is noted, as well as slight atrophy of the shoulder girdle and manual interosseus muscles. On opening the body cavities a complete situs transversus of the viscera is encountered. The peritoneal cavity contains some excess free fluid and many dense, fibrous adhesions about the gall bladder, the cecum, and the

pelvic portion of the small intestine. About the latter site there is also some fibrinous exudate. There are fibrous adhesions and about 800 cc. of fluid in either pleural cavity. The pericardium is universally adherent by fine, fibrous bands, with pleuro-pericardial adhesions on the right and some calcification. The heart weighs 420 gm. The muscle shows some scarring. On the posterior leaflet of the mitral valve in the line of closure are encountered two small, chronic, rheur ". The lungs show apical scars, bronchopneumonia and liver has a prominent nutmeg appearance. The gall bladder has a thickened wall and contains a number of stones under 2 mm. in diameter. The stomach mucosa contains numerous petechial hemorrhages. A segment 8 cm. long of the ileum is undergoing gangrene. The kidneys weigh 140 and 150 gm. Their surface is coarsely nodular, and the cut surface shows poor differentiation and obliterated and distorted markings. There are many patches of yellow scarring, and several small infarcts are noted. The intima of the aorta shows a few yellow plaques. No gross lesion of the brain is noted.

The gross *anatomic diagnoses* were: Situs transversus; fibrous pericardial adhesions; cardiac dilatation and hypertrophy; myocardial fibrosis; chronic rheumatic endocarditis; bronchopneumonia; pulmonary congestion and edema; fibrous pleural adhesions; apical pleural scars; hydrothorax, hydro-peritoneum, dependent edema; fibrous peritoneal adhesions; acute gangrenous enteritis; chronic cholecystitis and cholelithiasis; chronic passive congestion of liver; atrophy of spleen; multiple renal infarcts; vascular scarring of kidneys; fibrous thickening of left ureter; abdominal incisional hernia.

Microscopic Examination. Many of the smaller arteries and arterioles show a marked intimal fibroblastic proliferation with near-occlusion of the lumina, and in some instances canalization. There is fibrosis of the media, and marked wide perivascular scarring. A sparse infiltration of the walls of the vessels and perivascular tissues with lymphocytes, plasma cells and eosinophils is present. In many of the sections, especially in those of the heart, there are cells in the exudate which bear a high resemblance to Aschoff cells. The vessels of the following organs are affected: Kidneys, heart, stomach, gall bladder, gut, urinary bladder, pancreas, adrenals, voluntary muscle from the leg, and brain. There is some thrombosis in the intestinal vessels, and a gangrenous intestinal wall. Only an occasional small artery in the brain is affected. The gall bladder section shows in addition an acute ulceration of the mucosa.

Additional diagnoses included: Periarteritis nodosa; acute ulcerative cholecystitis.

Two further cases occurring on other services in the Wisconsin General Hospital are cited to emphasize the difficulties in the diagnosis of periarteritis nodosa.

Case Reports. CASE 2.—D. L. B., aged 69, was a white, male, retired merchant. The history was obtained from a son-in-law, since the patient's mental condition did not render the same reliable. For 3 months prior to admittance (June 11, 1929) the patient's mind had been failing. He would begin a sentence and then would be unable to complete it. Delusions of persecution were expressed and apparently these troubled the patient greatly. Although usually good natured, he became quite restless. The appetite had been good until recently. For the past few days the patient had been rubbing his head as if there might be pain, although no spontaneous complaint of this order had been volunteered. Several years ago the patient experienced some so-called asthmatic attacks and there was a recurrence within recent months with some cough. There has been a pro-

gressive weight loss of some 40 to 45 pounds in the past 3 years. An arrhythmia has existed for the past 2 years. There is a cathartic habit; recent incontinence of urine and feces has occurred. About 2 months ago there was a slight stroke, and later there had been muscle twitching without localization, lasting for hours at a time. The past medical history revealed only the "asthma" above-mentioned and chronic arthritis. A toe was amputated a year ago because of a beginning gangrene. The family history was irrelevant. The social history adds moderate use of alcohol and tobacco.

The physical examination revealed a rather uncoöperative individual. There was a marked arcus senilis; the extraocular movements could not be tested; there was a small amount of purulent material in the conjunctival sacs; the pupils were equal and slightly irregular; the eye grounds showed narrow, tortuous vessels, but there was no hemorrhage or exudate. The patient was edentulous, the tonsils were hypertrophied. The chest was emphysematous in type but no other pulmonary abnormality was established; the heart appeared enlarged to percussion; the second sound at the apex was ringing; there were no murmurs but an irregularity of rhythm occurred from time to time interrupting a regular rhythm; the peripheral vessels were thickened; blood pressure was 190/110; there was some tonal arrhythmia observed. The abdominal examination revealed no abnormality. The skin over the hands and wrists was glossy and deeply pigmented. The right hand was held in flexion and could not be extended. The right arm did not move voluntarily but the left arm and hand were used to accomplish all necessary movements; neither forearm could be extended completely at the elbow. There was pain upon movement of the hips, and the left great toe had been amputated. The biceps reflexes were hyperactive; but the patellar reflexes were definitely reduced and the Achilles reflexes could not be elicited. There were no paradoxical reflexes.

Laboratory examinations included a blood count which showed 76% hemoglobin, 0.7 color index, 4,950,000 red blood cells, 8400 white blood cells with 70% neutrophils, 4% eosinophils, and 26% lymphocytes. Blood Wassermann reaction was negative, the blood chemistry showed 94 mg. % sugar and 41.1 mg. % non-protein nitrogen.

On the 5th day after admission the patient showed a rapid decline. There was much mucus in the throat, the pulse was of poor quality and irregular, and death ensued. The clinical diagnoses were arteriosclerotic cardiovascular disease, myocardial degeneration, hypertension, arteriosclerosis of the brain and cord with dementia.

Autopsy (June 16, 1929; Dr. G. Ritchie; 2 hours after death). The body is that of a fairly well nourished elderly white male. There is limitation of motion in the right elbow to about 135 degrees, apparently the result of a bony ankylosis. There are a few fibrous pleural adhesions on the right. The heart weighs 410 gm.; the coronaries are sclerotic and calcified; the muscle is brown, with many gray streaks. The lungs exhibit emphysema, apical scar, posterior congestion and patchy bronchopneumonia. The spleen is somewhat atrophied. The liver shows a prominent nutmeg appearance. The gall bladder wall is thickened and the mucosa is atrophic with adhering yellow granules. The kidneys weigh 160 and 150 gm., and have a fine uniformly granular surface interrupted by several small cysts; the cut surface shows a cortex about 1 mm. in width, fair differentiation, and obliterated markings. The prostate is somewhat enlarged and slightly boggy. The aorta is tortuous, inelastic, and contains many pearly and yellow plaques and some calcification.

Gross Anatomic Diagnoses. Small granular kidneys; chronic myocardial fibrosis; cardiac hypertrophy; bronchopneumonia; senile emphysema; obsolete apical tuberculosis; splenic atrophy; chronic passive congestion of liver; chronic cholecystitis; hypertrophy of prostate; arteriosclerosis.

Microscopic Examination. More or less throughout the series of sections there are prominent changes in the smaller arteries and arterioles. In these vessels there is prominent hyaline degeneration of the media and intima, replacement of intima by fibroblasts, and wide perivascular concentric scarring. The vessel walls and perivascular tissue show a more or less dense infiltration with lymphocytes, plasma cells, eosinophils, and a few neutrophils. There is a notable difference between the lesions in various vessels, some showing chiefly hyalin degeneration of intima and marked infiltration remaining. The sections of the following organs show these changes: Heart, kidney, stomach, appendix, gall bladder, spleen, aorta, prostate and urinary bladder. (It is regretted that microscopic examination of brain tissue was not made.)

Additional Diagnoses. Periarteritis nodosa; chronic pericarditis; purulent bronchitis; acute prostatitis; interlobular pancreatitis; atrophy of pancreas; chronic cystitis.

CASE 3.—J. P., white male, aged 68, farmer, was admitted to the Wisconsin General Hospital on January 30, 1935, complaining of swelling of the legs. The patient stated that his first evidence of disability dated from October, 1934, when he began to experience a feeling of fullness in the head accompanied by dizziness that came on while shredding corn. Two weeks after this time the feet and ankles were swollen and there was pain on motion. The feet felt peculiar by reason of numbness and stinging. The swelling increased progressively, especially over the past month and involved the legs up to the knees and more recently the hands. A dull, aching pain persisted in the legs. For the past few months there had been a gradual decrease in the acuity of hearing and this sense was suddenly lost about 3 weeks ago. Tinnitus has also been noted. The throat was dry at the onset and until 3 weeks ago the patient would cough up some mucus in the morning. Dyspnea has been apparent on exertion since the onset of the dependent edema. Precordial discomfort had been observed at night from time to time. The history by systems added the occurrence of marked limitation of vision in the left eye succeeding an injury 9 years previously; vision in the right eye had failed, particularly in the past few months. Epistaxis occurred twice in the week before admission. Palpitation and arrhythmia had been noted for a period of 6 months. There were night sweats at the onset of the present illness. The appetite has been very poor for the past 4 months. Belching and sour eructations were noted over this period. Vomiting had occurred during the period of present illness. Nycturia had also been noted. Marked weakness and an inability to walk had led to confinement to bed. There was a weight loss of 20 pounds during the present illness. The past medical history was without pertinent relation except for the accident to the left eye above stated and the laceration of the tendon in the left thumb at about the same time. The social history indicated the moderate use of alcohol and tobacco. Family history added nothing of note except diabetes in the father, who died at the age of 79.

Physical Examination. Marked emaciation and prostration, and loss of tissue turgor. A few macules were sparsely scattered over the body. There was lateral nystagmus. Evidences of failing vision on the right and almost complete blindness on the left were noted; the left lens appeared opaque; the pupils were irregular and did not react to light; the fundal vessels were tortuous and there was silver wiring of the arteries. There was some bony deformity of the left nostril and some dry crusting of blood on the side. Deafness in the right ear was observed, but the hearing on the left was relatively good. The patient was completely edentulous; the tongue was dry and covered with a brownish coat; the pharynx was injected and

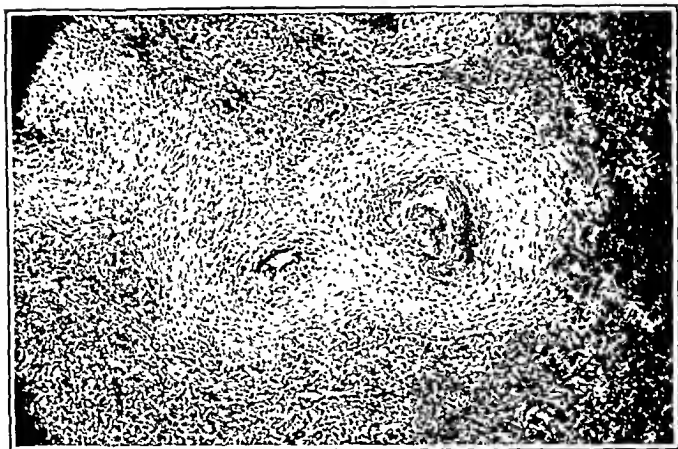


FIG. 1.—Case 1. Arcuate arteries of kidney, showing intimal coagulative necrosis in one, intimal fibroblastic proliferation, greatly reduced vascular lumina, and perivascular infiltration with plasma cells and lymphocytes. (Zeiss apochr. obj. 10, Homal II, $\times 60$.)



FIG. 2.—Case 1. Cut section of kidney showing generalized intense vascular scarring and infarction. (Reduced from actual size.)



FIG. 3.—Case 1. Small arteries in heart, showing hyperplastic intimitis, extremely narrowed vascular lumina, perivascular scarring, and sparse cellular infiltration. (Zeiss apochr. obj. 5, Homal I, $\times 45$.)



FIG. 4.—Case 1. Small arteries in gastrocnemius muscle, showing hyperplastic intimitis, perivascular scarring and diffuse infiltration with plasma cells, lymphocytes and eosinophils. (Zeiss apochr. obj. 5, Homal I, $\times 55$.)

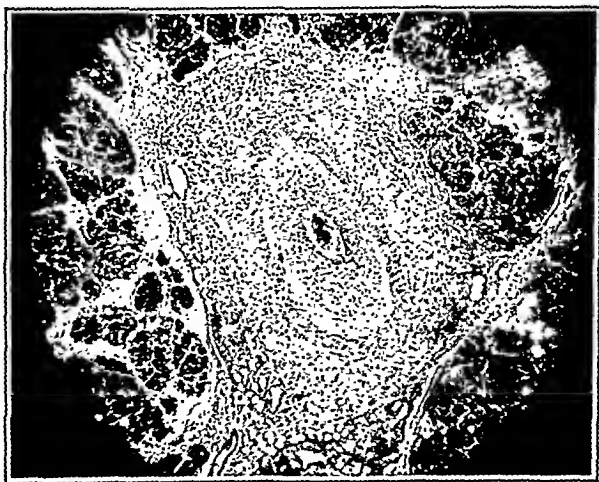


FIG. 5.—Case 1. Small artery in pancreas, showing marked hyperplastic intimitis and medial and perivascular scarring. (Zeiss apochr. obj. 5, Homal II, $\times 22$.)

strings of pasty mucus hung from the nasal pharynx into the oral pharynx; the tonsils were cryptic and markedly enlarged; the lips were pale and dry. A few palpable cervical lymph nodes were noted. The wasting of the muscles of the thorax was conspicuous. There was some lag in the respiratory movements on the left as compared with the right, and breath sounds were somewhat diminished in the left upper chest laterally. There were fine, moist râles in both bases posteriorly. The heart was apparently enlarged to the left upon percussion; there was a loud systolic murmur at the apex and along the left sternal border and a rough systolic murmur at the base over the aortic area; both aortic and pulmonic second sounds were accentuated. The blood pressure was 206/120. The peripheral vessels were markedly thickened and tortuous. Aside from a palpably enlarged liver no abnormality was established in the abdomen. Marked edema of both legs extended midway to the knees, and edema of the upper extremities as far up as the mid-forearm. Definite diminution of tactile perception was noted in the arms, legs and abdomen. Marked atrophy and loss of subcutaneous tissue was observed throughout. The deep tendon reflexes were normal in the upper extremities except for reduced radials; the abdominal reflexes were reduced; the knee jerks were definitely reduced and the Achilles reflexes absent; no paradoxical reflexes were established. Much pain was evinced upon rectal examination; the prostate was large and soft.

Laboratory Examinations. Urinalysis: Specific gravity ranged from 1.010 to 1.012, a trace of albumin, many coarsely granular casts and, in one specimen, a trace of blood by the benzidin reaction. Hemoglobin, 45%; color index, 0.6; red blood cells, 3,560,000; white blood cells, 10,150; neutrophils, 88%; small lymphocytes, 11%; and large mononuclears, 1%. The blood Wassermann was negative; on admittance the sugar was 113 mg. %; non-protein nitrogen 90 mg. %, and creatinin 2.4 mg. %. Eight days later the non-protein nitrogen had risen to 122 mg. %, and the creatinin to 2.6 mg. %. The phenolsulphonphthalein output was 15% in 2 hours. The total serum protein on admittance was 5.1 gm. per 100 cc.; the serum albumin was 2.37 gm., globulin 2.73 gm. %. Eight days later the total serum protein was 5.5 gm. %, the albumin 2.5 gm. %, the globulin 3 gm. %. The electrocardiogram the day after admittance showed normal rhythm, slight slurring of the Q-R-S complexes in Leads I and III, low T₁ and T₃. The intraventricular conduction time was 0.1 second and the auriculo-ventricular conduction time was 0.17 second.

The course during his hospital stay was complicated by a swelling over the right parotid gland with an area of inflammatory edema, sharply demarcated from the surrounding structures. There was no febrile reaction, although the pulse rate was accelerated. The leukocytes rose to 20,700 with 80% neutrophils, 13% small lymphocytes, and 7% large mononuclears. The absence of local erythema and the rapid resolution of the process argued against a diagnosis of erysipelas. On the 8th day of the hospital stay there was a sharp accession in the respiratory rate with an evident slump in the general condition of the patient, which taken with the presence of many fine, moist râles in the right apex, led to an impression of bronchopneumonia. In spite of supportive treatment, the patient rapidly went on to a fatal termination with advancing cyanosis and a failing circulation.

The clinical diagnoses were arteriosclerotic cardiovascular-renal disease, cardiac enlargement, myocardial degeneration, relative mitral insufficiency, atherosclerotic aortitis, hypertension, functional capacity IIb; nephrosclerosis of arteriosclerotic type with renal insufficiency. The other diagnoses were irrelevant.

Autopsy (February 9, 1935; Dr. G. G. Stebbins; 2 hours after death). The body is that of a poorly developed and nourished elderly white male.

There is some edema of the ankles and flanks. The peritoneal cavity contains about 100 cc. of clear amber fluid. The cecum is displaced and lies under the gall bladder, and the colon first descends and then ascends to become the transverse colon. There are fibrous pleural adhesions at the right apex, and the cavity contains 750 cc. of clear fluid. The left pleural cavity is obliterated by fibrous adhesions. The heart weighs 325 gm. and shows sclerosis of the coronaries, commissural adhesions of the aortic cusps and scarring of the muscle. The lungs are congested and edematous, and bronchopneumonia and an apical scar is present. The spleen has some sugar crust thickening of the capsule. The liver cut surface is nutmeg. In the jejunum and ileum there are dark hemorrhagic mucosal patches, some of which are definitely ulcerated. The largest of these is 7 by 2.5 cm., and the serosa opposite shows some plastic exudate. The kidneys weigh 160 and 150 gm. The capsule strips easily, leaving a smooth, irregularly mottled, yellow and reddish-purple surface; and the cut surface shows obliterated differentiation and markings, with a considerable amount of irregular proliferative change. The aorta has a moderate amount of senile sclerosis.

Gross Anatomic Diagnoses. Arteriosclerosis; myocardial fibrosis; chronic passive congestion of the liver and spleen; pulmonary edema, congestion and atelectasis; hydrothorax; ascites; ankle edema; bronchopneumonia; perisplenic fibrosis; ulcerations of small intestine; fibrous pleural adhesions; emaciation.

Microscopic Examination. The smaller arteries and arterioles in many tissue sections show a coagulative and hyalin necrosis of the media, a prominent fibroblastic proliferative intimitis, and an infiltration of the media, adventitia and perivascular tissue with neutrophils, eosinophils, lymphocytes and plasma cells. Many of the vessels are nearly occluded by the intimitis, and vessels in the intestinal wall show thrombosis. Vessels in the following organs are affected: Heart, kidneys, stomach, gall bladder, small intestine, spleen, urinary bladder, aorta and adrenals. The changes in the heart vessels are not prominent.

Additional Diagnoses. Periarteritis nodosa; thrombus in a pulmonary artery; vascular nephritis.

The etiology of periarteritis nodosa is unknown. Many surmises have been made, and some experimental work has been done, but as yet the pathologic characteristics of the disease seem to lend the surest guides as to the underlying cause.

Earlier writers often mentioned syphilis as the etiologic background; but since the development of the Wassermann reaction for diagnosis and the modern methods of treatment, any connection of the *Treponema pallidum* with the disease has been repeatedly disproved. Mechanical causes and parasites have been ruled out as etiologic agents; and the possibility of streptococcic septicemia has been disproved by repeatedly negative blood cultures.

There has been bacteriologic examination of the involved tissues and the blood of patients suffering with periarteritis nodosa by a number of workers from time to time, with uniformly negative results. The reports of Lamb¹² and Klotz³ in this connection are especially interesting. Von Haun in 1920⁵ believed that he had produced suggestive lesions in guinea pigs by injection of blood from a patient with periarteritis nodosa. In 1922 Harris and Friedrichs^{44,45} claimed to have transmitted the disease to rabbits by

material from lesions passed through a Berkefeld filter. Other workers have not been able to repeat their work, and indeed their published results are not convincing. However, Arkın¹¹ and Haining and Kimball,¹⁴ as well as some other recent writers incline to the belief that periarteritis nodosa is a specific disease entity, and offer a filterable virus as the probable etiologic agent, even though all attempts at isolation have failed to the present time.

In 1923 Ophüls⁴⁶ made a strong plea for the relationship of periarteritis nodosa and rheumatic fever, emphasizing clinical, pathologic and bacteriologic evidence. His summary of the evidence is excellent, and since that time strong confirmatory work has added strength to his position. The presence of lesions in smaller arteries in cases of acute rheumatic fever has received increasing comment; von Glahn and Pappenheimer⁴⁷ report "typical" lesions of this kind in 10 out of 47 cases of rheumatic fever which they reviewed. They believe that these lesions are to be distinguished from those of periarteritis nodosa, but the differential points quoted by them do not seem to us to be diagnostic. Friedberg and Gross,⁴⁰ in reviewing 8 cases of periarteritis nodosa, have shown the presence of typical Aschoff bodies in the myocardium in 4; and state that they believe that rheumatic fever is a common cause of periarteritis nodosa. They also comment, as have other authors, on the relationship of rheumatic fever, periarteritis nodosa and the malignant nephrosclerosis of Fahr to each other; and they offer as an explanation of "abdominal rheumatism" the lesions of periarteritis nodosa. One of the most recently reported cases of periarteritis nodosa⁴⁸ occurred in a patient suffering acute chorea, who was treated with salicylates, and in whom postmortem examination revealed acute myocardial and endocardial rheumatic lesions as well as those of periarteritis. The most consistently reported lesions accompanying periarteritis nodosa are those of rheumatic fever. In view, therefore, of the considerable evidence from many sources of the clinical, pathologic and bacteriologic relationship of rheumatic fever and periarteritis nodosa, the suggestion seems warranted that the latter be placed in the "rheumatic group."

Our cases of periarteritis nodosa exemplify certain of the problems in the clinical and pathologic definition of the disease. All 3 were males. This sex predominates in all reported groups. The age incidence covers a wide range, 3 months to 71 years; so that the ages of these patients, 48, 68 and 69 years, are scarcely significant. The duration of the terminal illness is difficult to fix. Curtis and Coffey¹⁰ give the range from 6 days to 6 years with an average of 16 months, but express the opinion that this figure is too high and favor Strong's⁴ figure of 5 months or Gruber's³⁹ of 4.7 months. The first patient of this group lived slightly over 4 months from the onset of symptoms, the second 3 months, and the third 4 months.

The intra-vitam diagnosis was rendered possible in Case 1 after a continued period of study by the complete evolution of the tetrad

of Meyer⁷ and Brinkmann.⁸ Vague to sharply localizing epigastric pain, headache, fever, polyneuritic and polymyositic manifestations were the earliest clues. Thereafter came the clear evidences of advancing renal involvement. A further interesting development was the occurrence of a diabetic sugar tolerance curve indicating pancreatic encroachment. The extreme eosinophilia in the differential blood picture was a further focusing detail. In this patient, as well as in Case 3, there was an inversion of the albumin-globulin ratio in the serum protein determinations. The clinical diagnosis was not made in Cases 2 and 3, and clearly the difficulties were much more serious than in Case 1. However, weight loss was an even more conspicuous manifestation in these two than in the first patient. In Case 2 the picture was that of central nervous system deterioration and the etiology was deemed to be simple arteriosclerosis, while in Case 3 renal insufficiency dominated the situation but distinct indications of a polyneuritis and possible polymyositis were overlooked or minimized. Arterial hypertension was added in the last case to direct attention more exclusively to the renal factor, a position supported by the laboratory evidences of renal incompetency. The latter 2 patients showed no such significant eosinophilia as in Case 1 during short periods of hospitalization. Subcutaneous nodules were not detected in any of the three and, as stated before, a biopsy of voluntary muscle in Case 1 was not diagnostic.

Without a clear insight into the etiology of periarteritis nodosa, treatment must be empiric. The experience of Carling and Braxton Hicks³⁷ and Schottstaedt¹³ in the response of such patients to arsphenamin must be unusual. Of course it need not be assumed that lesions responding to arsenicals are syphilitic; but the first named case did have associated syphilis. The trial of arsenicals is advocated without evidence of their specific value, even though many suggest their use only in the presence of recognized syphilis.

Lacking an accepted etiologic agent and specific therapy, the natural evolution of the disease attracts the attention. Many have assumed *a priori* that periarteritis nodosa is of necessity a fatal disease. Its clinical obscurity and the regularity of widespread histologic lesions at necropsy have supported this opinion. Carr²⁵ has ably analyzed this phase of the question, and Arkin¹¹ has traced the pathologic steps in the progression of the disease. Spiro¹⁹ refers to clinically latent and pathologically obsolete periarteritis nodosa. Klotz³ suggests the oversight of many cases through recovery. Schmorl³⁰ reports a case of the disease diagnosed by biopsy of a subcutaneous nodule that underwent a remission with antisiphilitic treatment. Two years later necropsy revealed only small fibrous foci in the kidneys, liver and heart as residuals of the earlier periarteritis nodosa. Probably the most unusual observation upon the evolution of the disease is that of Keegan⁴² previously cited. A right nephrectomy had been performed under conditions sug-

gesting a renal infection. The removed kidney presented arteriolar changes characteristic of periarteritis nodosa. Renal and circulatory incompetency succeeded this operation, and at necropsy 2 months later similar changes were observed in the cystic artery of the gall bladder, the pancreatic and the splenic arteries. The remaining kidney had undergone transformation to early arteriosclerosis and chronic vascular nephritis. This experience led Keegan to postulate that many cases of chronic vascular nephritis may have their origin in mild renal periarteritis nodosa.

Summary. From this review of the subject certain deductions regarding periarteritis nodosa seem reasonable:

1. The incidence of the disease probably greatly exceeds its recognition clinically and pathologically.

2. The pathology consists of a necrotizing arteritis, subacute and chronic cellular and fibrinous exudation, aneurysm formation, thrombosis, and fibroblastic proliferation and repair. The smaller arteries and arterioles are affected; and degeneration and infarction in the areas of supply are common.

3. Etiologically periarteritis nodosa is probably closely associated with the "rheumatic group" of diseases.

4. The tetrad of Meyer and Brinkmann, chlorotic marasmus, polyneuritis and polymyositis, striking abdominal manifestations (cramps, vomiting, diarrhea, melena and perforation) and nephritis, offers a logical foundation for the clinical appreciation and diagnosis of periarteritis nodosa.

5. Unexplained fever, polymyositis, polyneuritis and eosinophilia constitute peculiar grounds for the consideration of this diagnosis.

6. Wherever the question arises, recourse should be had to biopsy of accessible nodules or voluntary muscle.

7. Further study may grant diagnostic values to ophthalmoscopy, electrocardiography⁵⁰ and roentgenography of the lungs^{2b} in periarteritis nodosa as yet not clearly established.

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(Titles have been omitted for sake of brevity.)

PERIARTERITIS NODOSA (NECROTIZING PANARTERITIS) IN CHILDHOOD WITH MENINGEAL INVOLVEMENT.

REPORT OF A CASE WITH STUDY OF PATHOLOGIC FINDINGS.

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SINCE periarteritis nodosa is comparatively rare in adults, and particularly so in children, we have thought it worth while to report the following case which presents a number of interesting and

unusual features. A review of the literature of periarteritis nodosa in infancy and childhood was made by Rothstein and Welt,¹ in 1933, who abstracted 21 cases and added 2 cases of their own. In the same year, Nowak² reported an additional case in a child aged 12, and recently Friedberg and Gross³ have reported 2 cases associated with rheumatic fever in children, 1 of which had been previously reported by Rothstein and Welt.

Case Report. History. An Italian schoolgirl, aged 9, was admitted to the Long Island College Hospital on January 28, 1933, because of a purplish discoloration of the left ankle, pain in both legs, loss of weight and fever.

Six weeks before admission she injured her left ankle by striking it against a hard object. There was no discoloration, no swelling and no pain at that time. She was perfectly well until January 8, 1933, 20 days after the injury. She then complained of chilliness and pain in both legs. Her temperature was 102° F. by mouth. The next day she was unable to stand or walk because of the pain and remained in bed. She could move both legs but the motion was painful. These symptoms continued, and 7 days before admission the mother observed a small purplish discoloration on the outer surface of the left ankle. The discolored area gradually increased in size without any perceptible swelling. The pain in the legs became progressively worse and was most marked in the thighs and in the region of the left ankle. It was so severe that she was unable to sleep. She refused food but took liberal amounts of fluid without vomiting. The temperature fluctuated between 100° and 104° F. Because of the fever, loss of weight, pallor and the severity of the pains, she was brought to the hospital for treatment.

The father, mother, 5 brothers and sisters were living and well. The mother had had 2 miscarriages, apparently spontaneous. During infancy the patient had been poorly cared for. No cod-liver oil had been given during this period. At the age of 4 she developed pertussis of average severity. She had several colds each winter, with no complications. There was no history of tonsillitis, chorea, growing pains, arthritis or scarlet fever. The mother stated that she was backward at school.

Physical Examination. The temperature was 103.8° F., pulse 106 and respirations 28 per minute. The child was acutely ill, pale and apparently in severe pain. She was restless and irritable. There had been considerable loss of weight. She rested on her side with the lower extremities drawn up against the abdomen.

The skull showed no abnormalities. The eyes were somewhat sunken. The pupils were equal and their reactions normal. The ears were normal. There were herpetic lesions on the lower lip. The mucous membranes of the nose and mouth were pale, the tongue was coated and dry and there were many carious teeth. The tonsils were small and the pharynx was reddened but no exudate was noted. There was no enlargement of the cervical lymph nodes. The chest was symmetrical and narrow. The lungs were apparently normal. The heart sounds were regular and strong and there was no evidence of enlargement. A soft, apical systolic murmur was present but was not transmitted. The abdomen was flat and showed a moderate degree of generalized tenderness and rigidity. The liver and spleen were apparently normal in size. No abnormal masses were palpable. The external genitalia were normal.

The upper extremities were normal, the lower symmetrical and there was no edema. The veins of the ankle and dorsal surface of the left foot seemed more prominent than is usual in a child of this age. To a lesser extent this was also true of the right extremity. Any attempt passively to move

the lower extremities was accompanied by severe pain. The joints seemed to be normal. Pain was elicited when pressure was applied to the thighs. An extremely tender, not elevated ecchymotic area, about 4 cm. in diameter, was found over the external malleolus of the left ankle. The reflexes were equal and active on both sides. No pathologic reflexes were elicited.

Laboratory Data. The red blood cell count was 4,240,000 per c.mm., and the hemoglobin was 54% (Sahli). There were 20,500 white blood cells per c.mm., with 83% neutrophils, 13% lymphocytes, 2% mononuclear and 2% eosinophils. The bleeding and coagulation times were normal. The platelets numbered 230,000 per c.mm. The blood and spinal fluid Wassermann reactions were negative and the spinal fluid cytology and pressure were within normal limits. Non-protein nitrogen and sugar determinations of the blood were normal. The blood culture and Widal reactions were negative. A roentgenologic study of the left ankle, pelvis, hip joints and lower spine showed no abnormalities.

COURSE. The course of the child's illness was that usually seen in general sepsis. The temperature fluctuated between 101° and 104° F. The pulse continued regular but very rapid. There was no change in the systolic murmur. Generally, except for loss of weight, the physical findings did not differ from those elicited at the initial examination. However, 8 days after admission the ecchymotic area on the left ankle increased to about 6 by 4 cm. in size. Several small ecchymotic areas also appeared on the ankle, dorsum of the left foot, the inner surface of the left leg and the plantar surface of the right foot. Several blebs contained a serosanguineous fluid developed on the skin of the left ankle over the largest of these lesions. Culture of this fluid revealed a hemolytic *Staphylococcus aureus*. Two days after their appearance the blebs ruptured and left an ulcerated area from which a serosanguineous fluid continued to exude. There was now a loss of pain and temperature sense distal to the ecchymotic area on the left ankle, while directly over this area these sensations were diminished. Treatment did not change the appearance of these lesions.

Two weeks after admission laboratory studies revealed a red blood cell count of 3,900,000 per c.mm. and a hemoglobin of 65% (Sahli). The white blood cells numbered 19,200 per c.mm., with 84% neutrophils and 16% lymphocytes. The urine showed a trace of albumin, a few pus cells but no red blood cells and no casts. Repeated blood cultures continued to show no growth.

Despite supportive and symptomatic treatment the child became progressively worse, and 15 days after admission she developed a clonic convulsion of the left arm and left side of the face, which soon involved the entire body. Spinal puncture showed an increase of pressure, but no changes in the cytology or chemistry of the spinal fluid were found. The systolic blood pressure was 115 mm.; the diastolic pressure could not be obtained. The convulsions ceased the following day and were replaced by a rigidity of the decerebrate type. The patient remained in coma and died 2 days later without regaining consciousness.

The presence of bizarre symptomatology and the absence of definite laboratory findings made the diagnosis of this case most difficult. The opinion was expressed, however, that we were dealing with a widespread vascular lesion of undetermined nature.

NECROPSY. The body was that of a fairly well-developed but poorly nourished, white, female child. On the lateral and posterior aspects of the left ankle there was a large ulcerated area, with an ecchymotic border, which measure 8 cm. in length, 4 cm. in width, extending through the superficial fascia to the peroneus tendons (Fig. 1). No gross evidence of infection of this area was noted. In the immediate vicinity there were a few small reddened ulcerated areas, measuring from 5 to 10 mm. in diam-

eter, which were covered by dark red crusts and surrounded by brownish-purple zones apparently subsiding ecchymoses. There was no swelling of the soft tissues, bone or joint in this region. The plantar surface of the right foot showed several small ecchymotic spots, measuring from 2 to 4 mm. in size. No other abnormalities were noted on external examination.

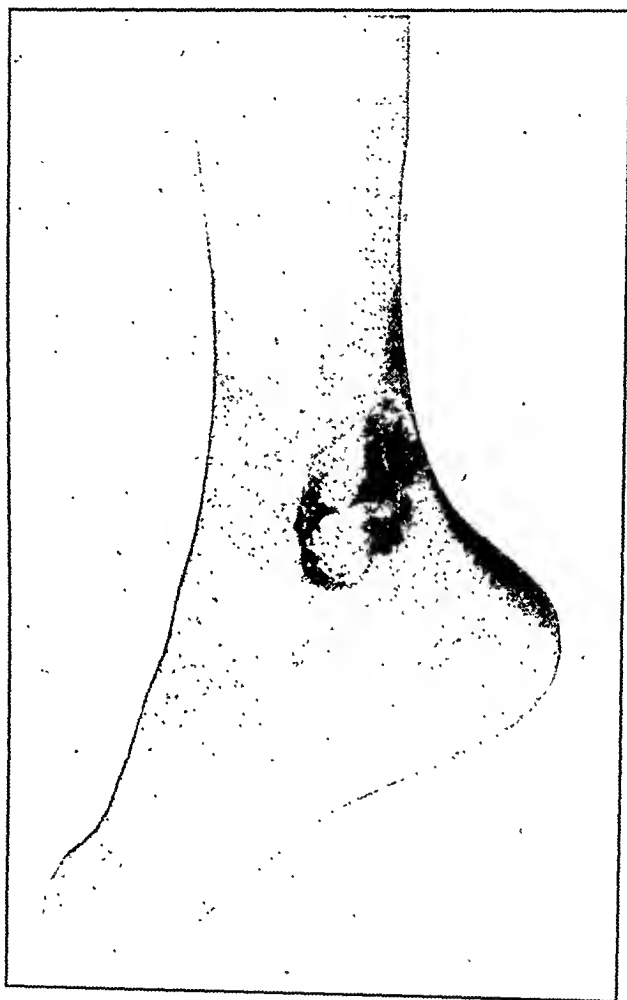


FIG. 1.—Photograph of left ankle, showing ulceration over external malleolus with surrounding ecchymotic arcs. The peroneus tendons can be seen in the posterior portion of the ulcer.

Each pleural cavity contained 50 cc. of clear yellow fluid. The surfaces were free of exudate. The lungs showed passive congestion and edema, and their combined weight was 955 gm. No gross lesions of the pulmonary bloodvessels could be found.

The pericardial sac contained 30 cc. of blood-tinged fluid. The pericardial surfaces were smooth and glistening. The heart weighed 250 gm. (normal weight for 9-year-old female, 110 gm.). The myocardium, except for slight hypertrophy of the right ventricle, was essentially normal. On the auricular surface of the anterior mitral leaflet, along the line of closure, a nodular ridgelike elevation, measuring 1 mm. in height, was noted. On

the posterior leaflet there were several grayish-white nodules, measuring from 1 to 2 mm. in diameter. Grossly the appearance was that of a healed rheumatic endocarditis. The remaining valves showed nothing of pathologic significance.

The abdominal cavity was bathed in a greenish-brown, sour-smelling fluid, of which there was 90 cc. in the pelvis. The serous surfaces were found covered with a fibrinous exudate. On the lesser curvature of the stomach, 2 cm. from the pylorus, there was a perforated ulcer, measuring 1 cm. in diameter. Another small ulcer, but non-perforating, was found at the pylorus and still another in the first part of the duodenum. The remainder of the gastro-intestinal tract was normal except for several small petechial hemorrhages in the mucosa of the transverse colon and lower ileum.

The liver was about normal in size, weighed 540 gm. (normal weight, 750 gm.⁴) and was reddish-brown in color. The surface presented numerous irregular depressed yellowish areas, surrounded by hemorrhagic zones. These areas almost entirely covered the superior and inferior surfaces of the left lobe. On section, areas similar to those seen on the surface were found, and in the portal areas there were numerous small gray translucent nodules resembling tubercles. The vessels in the portal canals were unusually prominent and markedly thickened, the lumina of some being almost completely occluded. In some instances thrombi were found in the vessels.

The spleen was about normal in size and weighed 70 gm. (normal weight, 60 gm.⁴). The capsule was thin and on the surface irregular depressed yellowish areas were found. Similar areas were found on the cut surface.

The kidneys were slightly enlarged and together weighed 145 gm. (normal weight of each, 120 gm.⁴). Their external and cut surfaces presented numerous small yellow patches surrounded by hemorrhagic zones. The interlobular and arcuate arteries were thickened, gaping and in some instances occluded.

The adrenals were essentially normal except for several small pin-point orange-yellow nodules found in both the cortex and capsule.

The pancreas was grossly normal except for a moderate degree of thickening of the vessel walls.

On opening the skull, the dura was found to be normal. The leptomeninges were congested and a slightly increased quantity of opalescent subarachnoid fluid was found. The vessels at the base of the brain appeared normal. The cerebral convolutions were slightly flattened and the sulci somewhat narrowed. Sections through the brain showed no gross pathologic changes. The dural sinuses contained fluid blood and appeared normal.

The pituitary body was normal in size but markedly congested.

In the ethmoid sinus a small hemorrhagic erosion of the mucous membrane was found.

The right eye was removed and found normal in size and shape. The cornea was slightly "steamy," so that no details of the inner structures could be seen. After fixation "windows" were cut in the horizontal plane. The retina was not detached and, moreover, gave the impression of being abnormally adherent. Otherwise the organ appeared grossly normal.

Culture of the blood taken at autopsy revealed no bacterial growth.

MICROSCOPIC EXAMINATION. The most striking lesions were found in the small and medium-sized arteries of the kidneys, liver and spleen and the superior mesenteric artery. The media of most of these arteries showed both degenerative and inflammatory changes. The mildest changes noted were edema of the media and swelling of the muscle cells. Other lesions apparently more advanced showed a thready fibrinous exudate in both

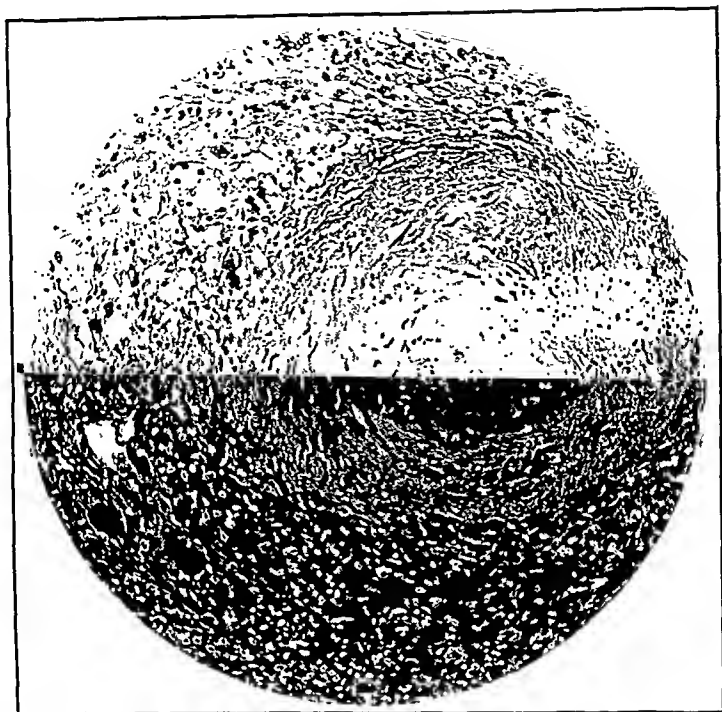


FIG. 2.—Section of small artery, showing destruction of media with hyalinization and infiltration of adventitia and periadventitial tissue with epithelioid cells and round cells. One very large and several smaller Langhans' giant cells are shown.



FIG. 3.—Section of brain and pia-arachnoid in a sulcus, showing congestion, edema and moderately heavy infiltration with round cells. There is marked margination of leukocytes in bloodvessels.

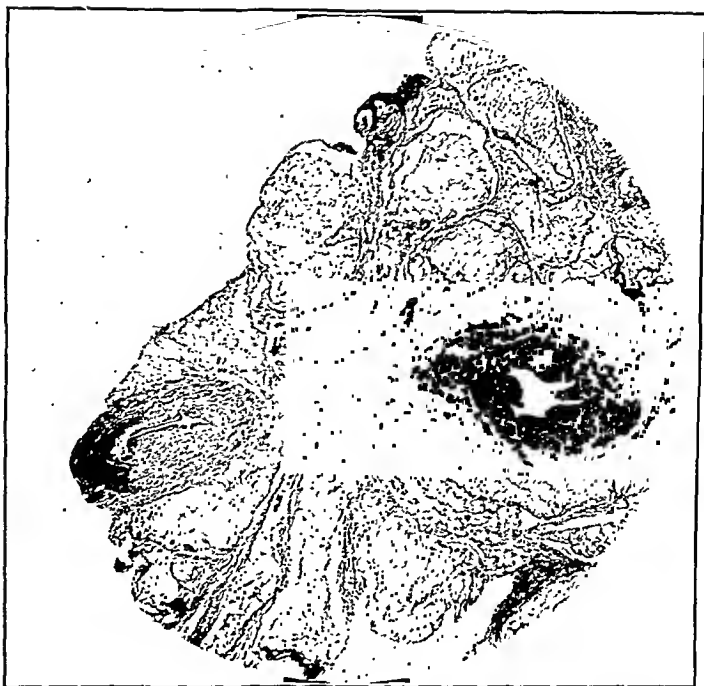


FIG. 4.—Section of margin of skin ulcer, showing two arteries with marked irregular intimal thickening and replacement of media and adventitia with granulation tissue.

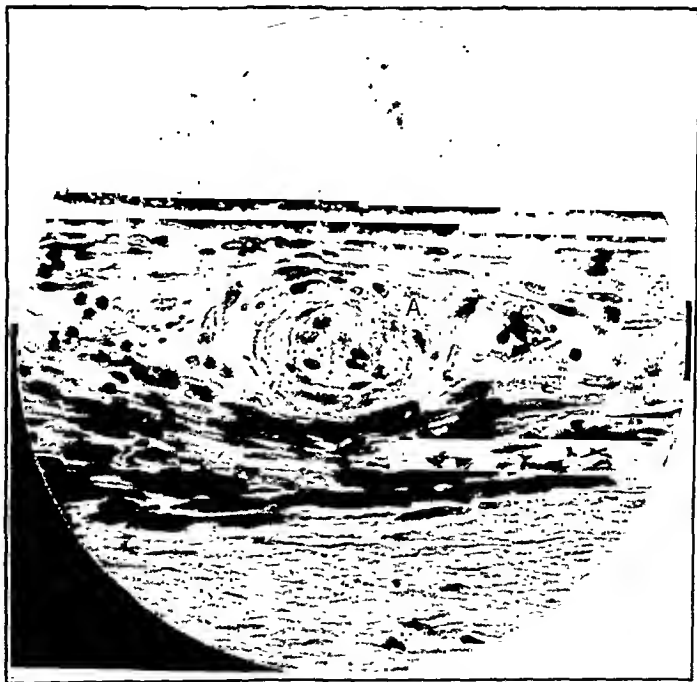


FIG. 5.—Section of eye, showing vascular changes and cellular infiltration in the choroid. At A is seen a small thrombosed artery with many leukocytes in the thrombus. The retinal separation in this region is an artifact.

the inner and outer portions of the media. Arteries more severely damaged showed coagulation necrosis of the media and hyalin degeneration. This necrotic process involved, in some arteries, the intima and adventitia, and in some instances was associated with hemorrhage throughout the entire vessel wall. In many of the arteries the necrotic and degenerated areas were infiltrated with moderately large numbers of neutrophils and lymphocytes and a few plasma cells. In other vessels showing these marked changes saccular aneurysms, measuring from 0.5 to 1 mm., were found, some of which had ruptured, giving rise to perivascular hemorrhages. An almost constant finding was intimal thickening or occlusion of the lumina as a result of intimal proliferation (Fig. 2). In the latter instance it was at times impossible to differentiate proliferated intima from recanalized thrombi except for the presence of the latter. The adventitia of some arteries showed and, as previously mentioned, was also frequently involved in the degenerative, necrotic and acute inflammatory processes.

The degenerative and acute inflammatory changes in the walls of some of the vessels were associated with the formation of granulation tissue, apparently replacing the necrotic areas. In such lesions the neutrophilic infiltration was less marked. However, in some arteries so involved there was also evidence of recent medial necrosis, in addition to the granulation tissue and intimal proliferation, suggesting acute exacerbations of the process.

A feature in the histologic examination was the finding of the areas of granulation tissue in and around the adventitia of the affected vessels. In many of these areas giant cells of the Langhans type were seen. The giant cells varied in size and contained from 6 to 10 nuclei. These lesions, which resembled granulomata, were most numerous in the kidneys and spleen.

The parenchyma of the liver and kidneys showed generally various stages of epithelial degeneration. Typical infarcts were found which were infiltrated with moderate numbers of neutrophils, lymphocytes and a few plasma cells, and surrounded by hemorrhagic zones. The spleen also showed areas of infarction.

The heart presented a round-cell infiltration of the myocardium, the muscle cells of which showed parenchymatous degeneration. Scattered throughout the myocardium were small irregular patches of edematous connective tissue in which a few necrotic remnants of muscle cells could be discerned. There was a moderate to marked degree of intimal proliferation in the smaller branches of the coronary arteries. Necrosis as well as necrobiotic changes were found in the media and there was an adventitial and periadventitial proliferation of fibroblasts and infiltration of lymphocytes and plasma cells. In the subepicardial fat one of the larger branches of a coronary artery showed a considerable degree of necrosis and round-cell infiltration of the media. In one area this necrosis was extreme, with thinning of the wall and beginning aneurysm formation. The atrial surface of the endocardium of the mitral valve was thickened by edema and connective-tissue proliferation and was infiltrated with lymphocytes. The small arteries in the valve showed perivascular round-cell infiltration and intimal thickening. The vascularity of the valve, however, was considered normal for a child of this age. The cellular infiltration was most prominent at the bases of the small nodular excrescences, noted grossly forming an elevated ridge along the closing margin of the valve. These excrescences consisted of hyalinized collagenous fibers, with few fibrocytes, infiltrated with moderate numbers of lymphocytes and covered by a layer of endothelium. No Aschoff bodies were found in the myocardium or valves.

The intima of the aorta showed slight connective-tissue proliferation.

In the media a few scattered light blue staining oval areas of necrosis were found. The vasa vasorum in the outer third of the media were increased in number and presented a perivascular round-cell infiltration and intimal proliferation. The vessels of the adventitia were also thickened, and in some places their lumina were obliterated either as the result of intimal proliferation or thrombus formation. In some areas the adventitia as well as the outer third of the media was infiltrated by lymphocytes and a few plasma cells.

The lungs revealed no pathologic lesions of significance in either the parenchyma or vessels.

Sections of the stomach showed arterial lesions similar to those observed in the liver and kidney. The walls of the perforated ulcer showed necrosis of the entire thickness of the mucous membrane and were also found to be infiltrated with neutrophils, lymphocytes and a few plasma cells. The mucous membrane from various other sites showed atrophy, degeneration or necrosis of the epithelium. The muscularis appeared edematous and showed small areas of degeneration. The serosa was covered with a layer of exudate consisting of fibrin and pus cells.

The duodenum presented an ulcer which extended into the inner portion of the submucosa, the outer half of which showed considerable edema. An acute inflammatory reaction was noted in the tissue surrounding the ulcer. The muscularis and serosa were congested and edematous and the former showed small areas of necrosis. In the subserosal coat a medium-sized artery showed degenerative and inflammatory changes and its lumen contained a recanalized thrombus. Smaller arteries in this region also showed changes similar to those first described.

The pancreas showed nothing of pathologic significance except a moderate degree of arterial intimal proliferation, degenerative changes of the media and perivascular fibroblastic proliferation. No inflammatory changes were found.

The arteries of the adrenal capsule revealed lesions similar to those described in the kidney, liver and spleen. Numerous recanalized thrombi were found filling the lumina of many arteries. The collections of sympathetic ganglion cells showed various stages of degeneration. Focal areas of necrosis were noted in the cortex. The medulla also showed scattered areas of degeneration and necrosis of its cells.

The leptomeninges were edematous, moderately congested and infiltrated with moderate numbers of lymphocytes and plasma cells (Fig. 3). The arteries of the meninges showed degenerative and necrotic changes of the media. The ganglion cells of the cerebrum showed a marked degree of cloudy swelling, eccentricity of the nuclei, chromatolysis, or necrosis with extrusion of nuclei and a slight degree of satellitosis. Small arteries of the brain showed both degenerative and necrotic changes in the media, intimal proliferation and perivascular collections consisting of lymphocytes, a few plasma cells and an occasional neutrophil. There was a considerable degree of edema throughout the brain substance.

The pituitary appeared markedly congested and edematous, and in several areas there were small patches of necrosis, presumably infarcts. The vessels of the surrounding dura showed intimal thickening and an occasional organized thrombus.

Sections through the margin of the ulcer of the leg showed atrophy and necrosis of the epidermis. The corium was edematous and infiltrated with round cells. In the floor of the ulcer a medium-sized artery showed a moderate degree of intimal proliferation, medial necrosis and acute inflammatory infiltration throughout its entire thickness. At one point this artery was ruptured. The smaller arteries showed rather marked intimal proliferation (Fig. 4), degenerative changes in the media and collections

of inflammatory cells in both the media and adventitia. Clumps of bacteria were found in the necrotic material lining the ulcer.

Microscopic examination of eye (Dr. J. A. deVeer): The cornea was found to be the seat of a healing ulcer in which there was irregular regeneration of the surface epithelium, focal destruction of Bowman's membrane and light leukocytic infiltration of the corneal stroma. There was also a subacute and chronic iridocyclitis, as shown by cellular infiltration of the iris and ciliary body with exudation into the aqueous chambers, and synechiæ between the pupillary portion of the iris and the lens capsule. The lens was otherwise normal.

The most marked changes were seen in the choroid, which also was the seat of subacute and chronic inflammation. The vessels here showed thickening of their walls with narrowing or complete occlusion of their lumina. An occasional artery showed a thickened intima infiltrated with neutrophils and lymphocytes. Perivascular mantles of lymphocytes were found about many of the vessels. The choroidal stroma was atrophic and fibrotic, with a light mononuclear and neutrophilic infiltration (Fig. 5).

The attachment of the retina to the choroid was firmer than usual. There were no changes of note in the retinal vessels. The macula was edematous and the fovea centralis atrophic. The optic nerve showed mild inflammatory changes.

There was also a subacute and chronic episcleritis and orbital cellulitis. The arteries and arterioles in these tissues were thickened and in many the lumina were narrowed or occluded.

The eye changes may be summed up as those of subacute and chronic uveitis, episcleritis and orbital cellulitis. The vascular lesions were of the same order as those in other organs, but with less acute degenerative and inflammatory features. The ulceration of the cornea may have been in part or entirely the result of lagophthalmos.

Discussion. The term "necrotizing panarteritis" is suggested as being descriptive of the lesions in this arterial disease and, therefore, preferable to the older designation "periarteritis nodosa." The lesions are not nodose but extend over extensive segments of the affected arteries, as may be demonstrated by serial sections. They are not purely perivascular in location but involve all the coats of the affected arteries as well as the perivascular tissue in an extensive necrotizing process.

The lesions encountered in our case fit well into the classification of Arkin,⁵ who divides the disease into a degenerative, an acute inflammatory, a granulation tissue and a healed stage. A few of the vascular lesions in our case were degenerative, some were inflammatory, but the majority were of the granulation tissue stage. We were unable to find any examples of the healed stage. In some instances, apparently because of the rapidity of events and because of acute exacerbations of the process, all three stages were found in the same artery. It is, therefore, impossible to say which coat was the seat of the earliest change. If the presence of a hyalin eosin staining band is to be accepted as characteristic of the initial stages of the vascular lesion, then this zone was found in our case to be located chiefly in the media of the vessels.

The perivascular and adventitial nodules produced by proliferative changes, and containing epithelioid cells, giant cells and round

cells, have a striking resemblance to the infectious granulomata. Ophüls,⁶ in his discussion of periarteritis nodosa, refers to these lesions as granulomata, and mentions that Aschoff noted their resemblance to those found in rheumatic fever. The former author stated that giant cells were not found in the nodules but only in the media. In our case, however, giant cells were found in both the nodules and media. Haining and Kimball,⁷ in a recently reported case of periarteritis nodosa, have noted the occurrence of numerous giant cells around the affected arteries in the kidney.

The presence of a leptomeningitis in this case is of particular interest, since no instances of meningitis primarily due to periarteritis nodosa have been previously reported. In adults, meningitis has been mentioned in 2 cases. In 1 of these (Haining and Kimball⁷) the meningitis was due to a complicating pneumococcus infection and bore no causal relation to the primary disease. In the other (Bennet and Levine⁸) there were clinical signs of meningitis, but these were not supported by anatomic findings. In several other cases, 3 in children, although there were clinical manifestations of cerebral involvement and meningeal irritation, the lesions found at autopsy were hemorrhage into either the brain or the meninges from rupture of aneurysms or softening of the brain due to thrombosis.

The occurrence of a gastric and a duodenal ulcer with perforation of the former and a resulting acute peritonitis is also of interest, since, in children, no cases with these manifestations have been reported.

Ulceration of the skin in children has been reported in only 2 previous cases (Debre,⁹ Hutinel¹⁰). In these the ulceration appeared, respectively, on the tenth and seventh days of the illness. In our case the ulceration was extensive, involving the deeper portions of corium and superficial fascia with typical periarteritic lesions in the base of the ulcer and surrounding tissues. The fact that the ulceration in this instance was preceded by injury to the involved area, with persistent ecchymosis and deep tenderness, gave rise to clinical suspicions of underlying bone disease.

The relationship of this disease to rheumatic fever has been suggested by several authors, and most recently by Friedberg and Gross,³ who report the occurrence of periarteritis nodosa associated with rheumatic fever and rheumatic heart disease in 4 cases, 2 of which were in children. These authors, therefore, suggest rheumatic fever to be "a common cause of the vascular lesions, termed periarteritis nodosa." In our case there were lesions on the mitral valve which were interpreted as rheumatic verrucous endocarditis, though no Aschoff bodies were found. Apparently rheumatic heart disease and periarteritis nodosa are not uncommonly associated. Whether or not this is due to causal relationship must be determined by further study.

Opportunities for histologic examination of the eyes in cases of periarteritis nodosa have been rare, and the findings of characteristic arterial lesions in this case in both the bulb and orbital tissue is of especial interest.

It is to be noted that there was a paucity of symptoms referable to the parenchymatous organs when compared to the widespread involvement of these organs, particularly the kidneys.

Summary. 1. A case of necrotizing panarteritis (periarteritis nodosa) in a girl, aged 9, is presented.

2. The widespread vascular lesions correspond to the degenerative, inflammatory and granulation tissue stages of this disease, as described by Arkin.

3. A primary subacute leptomeningitis due to periarteritis nodosa is described. No other cases of primary meningitis either in children or adults have been reported.

4. The occurrence of unusual features, such as gastro-intestinal ulceration with perforation and peritonitis, ulceration of the skin following injury and the occurrence of ocular lesions has been briefly discussed.

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PERIARTERITIS NODOSA WITHOUT PERIPHERAL NODULES DIAGNOSED ANTEMORTEM.

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ALTHOUGH an uncommon condition, periarteritis nodosa is of interest from several aspects. To the clinician, the protean manifestations of the disease are a challenge to his diagnostic acumen.

By virtue of the microscopic resemblance to more frequently encountered conditions such as rheumatic fever and typhus fever, periarteritis nodosa appeals to the imagination of the pathologist. To both groups the problem of the etiology of this almost inevitably fatal disease, is of importance.

The various clinical types of periarteritis nodosa have been described frequently. Nevertheless, an antemortem diagnosis has been excessively rare, and such of these as have been made were usually the result of a biopsy performed to establish the suspected presence of some other disease such as trichiniasis or dermatomyositis. An occasional case has been recognized at operation with the finding of nodules in the abdominal cavity, or again, upon microscopic examination of an excised organ. A correct clinical diagnosis has not been made more often either because of too great emphasis on a single group of findings to the exclusion of other important ones, or else because of the confusion aroused by the multiplicity of bizarre symptoms.

The present report is concerned with a case of periarteritis nodosa without peripheral nodules, in which the diagnosis was suspected and verified by biopsy of a muscle, before death. This is the first instance of such a case thus directly established, that I have been able to find in the American or English literature.

Case Reports. CASE 1.—R. S., a white, male mechanic, aged 44 (Unit No. 51766), was admitted to this hospital on October 14, 1933, complaining of fever, chills and pains in the extremities. His father died at 74 of hypertension; his mother at 70 of a stroke. The patient's general health had been excellent. He had had the usual childhood diseases including scarlet fever. At 25 he suffered a mild attack of pneumonia. In 1923 there had been a traumatic ulcer on the left shin which was slow in healing. In 1931, as the result of a fall, he broke several ribs on the left side. At the age of 20 he had contracted a gonorrheal infection. There was no history of primary or secondary syphilis, but 18 years before he had received an inadequate course of antiluetic treatment: about 12 injections in all. He had 5 living children; his wife had had no miscarriages. His habits were temperate. For several years he had known of an existing hypertension, the systolic pressure sometimes attaining a level of 220 mm.

In January, 1933, he was first seen in the outpatient department where he appeared with the complaint of lumbar pain. He was found to have a blood pressure of 212/114 mm., normal temperature, and a pulse rate of 92. There was a skin eruption, interpreted as lichen planus, over the body. The urine contained a trace of albumin and microscopically, pus cells and bacteria. The Wassermann reaction was positive. Roentgen ray showed no enlargement of the heart or aorta. He was started promptly on antiluetic treatment consisting of alternating courses of bismuth and neosphenamin. To this schedule he adhered until October 1, 1933.

The patient dated the onset of his present illness to early September, 1933. Detailed inquiry, however, elicited more remote relevant facts. During the winter of 1930 he had had several transient attacks of numbness and blanching of the fingers of both hands, more marked on the left. He recalled 3 or 4 attacks of amblyopia in the left eye of brief duration in the summer of 1933. On September 7, 1933, he was seized with occipital aching, pains in the shoulders, wrists and lower extremities. There were



FIG. 1.—Artery in a muscle from Case 1. ($\times 90$.)

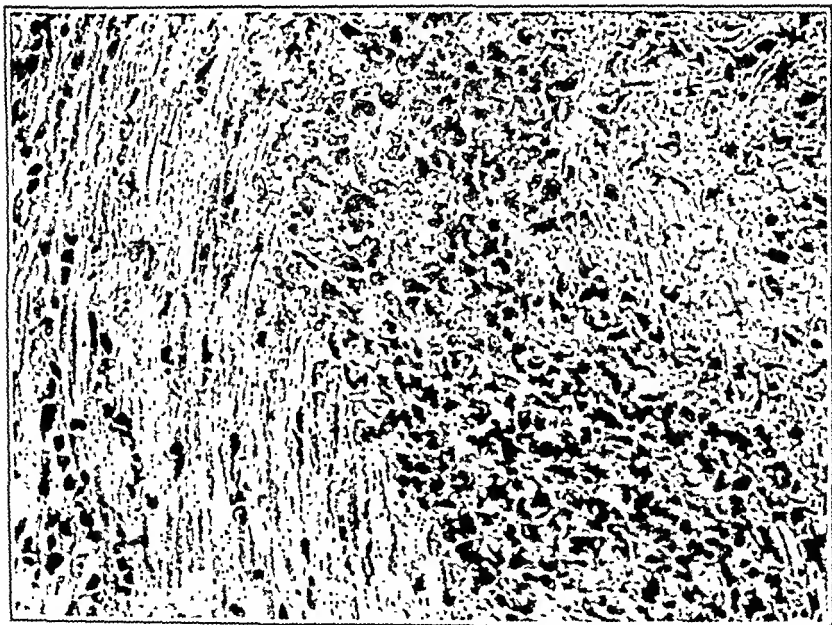


FIG. 2.—Intima and media of same vessel. ($\times 350$.)

chills and sweats in the following days, with fever as high as 101°. He became weak and lost weight. Just before he was forced to bed, after 3 weeks of continuous distress, his blood pressure had fallen to 140 mm. systolic. Following this the pains disappeared but weakness progressed and he lost about 15 pounds in a few weeks. Bilateral increasing deafness now set in. Three days before admission there appeared numbness and paresthesias of the right hand followed a day later by similar symptoms of the left hand.

On admission, October 14, 1933, his temperature was 103.8°, pulse 108, blood pressure 155/90 mm. He appeared chronically ill. There was conspicuous loss of weight. His hearing was impaired by a disturbance of nerve conduction. The fundi revealed minimal arteriolar changes. Pupils were irregular but reacted promptly to light. Examination of the heart and lungs showed no notable abnormalities. Both the liver and the spleen were just palpable. Over the hands there were areas of hypæsthesia, involving the ventral surfaces of both hands as well as the dorsal surface of the right. No motor weakness was made out. Reflexes were normally elicited save for the abdominals and cremasterics.

The erythrocyte count was 4,340,000; hemoglobin 80%; leukocyte count 13,300; neutrophils 91%, eosinophils 3%, lymphocytes 6%. The urine showed only an occasional white blood cell. A blood culture was sterile as were several subsequent ones. The Wassermann reaction was positive. A Widal reaction as well as agglutination tests for melitensis and suipestifer were entirely negative. From the urine *B. coli* was cultured.

During the first 4 days in the hospital the patient's fever was remittent, attaining peaks of 104°. For the next 3 weeks it ranged between 100° and 102°; then for 2 weeks between 99° and 101°; for the final period it remained under 100°. The pulse rate varied between 100 and 120, usually being out of proportion to the temperature. His illness at first was characterized by drenching sweats. Ten days after admission a right footdrop appeared. About the same time it was noted that there was edema of the legs and back as well as ascites. He became weaker and continued to lose weight. A footdrop appeared on the left side as well as a right wristdrop. There was tenderness to pressure on the calf muscles and definite atrophy of the muscles of the hands. Early in November he began to complain of lower abdominal fullness. On November 10 the patient awakened to find that he was blind in the left eye. The cause for this was found to be an occlusion of the central retinal artery. Sensory disturbances in the hands, feet and about the right ear persisted. His blood pressure which had dropped as low as 138 mm. systolic shortly after admission began slowly to rise once more, attaining a level of 228/134 mm. on January 18, 1934. A moderate anemia developed, the hemoglobin falling to 70%. The leukocytes maintained a level of 12,000 to 13,000, rising above 14,300 only terminally. Eosinophils averaged 5% but at one time were as high as 13%.

The bizarre combination of findings—weakness, emaciation, fever, peripheral neuritis, abdominal pain, anemia with eosinophilia, the retinal vascular occlusion, the variable blood pressure—suggested the possibility of periarteritis nodosa, even though no nodes were ever discovered along the peripheral vessels. A piece of the left gastrocnemius muscle was therefore removed on November 22, 1933 for microscopic examination. The muscle was found to show scattered areas of atrophy. The veins were normal but the arteries showed a thickening of all coats associated with round cell infiltration and fibrosis. No definite thrombi were found although the lumina were quite narrowed. About the vessels there was a small amount of round-cell infiltration, mostly plasma cells with a few eosinophils. The media was not remarkably thickened but contained a few round cells. The intima showed the greatest relative thickening. A hyalin ring marked

the innermost portion of this coat. This picture was considered to be characteristic of periarteritis nodosa (Figs. 1 and 2).

In December edema became a more conspicuous feature. The patient had been receiving potassium iodid for some weeks. This was stopped and digitalis was given. By January the patient was reduced to a vegetative existence. He could move neither hand nor foot. His mental processes were dulled and he took no interest in his surroundings. Incontinence developed followed terminally by acute retention. At the end, the non-protein nitrogen, previously normal, rose to 90 mg.%. With a final fall of blood pressure on January 22, 1934, he died quietly, 4½ months after the onset of his acute illness. Autopsy permission was not obtained.

Additional laboratory studies provided nothing of importance. The urine contained traces of albumin, a few red blood cells and casts. The spinal fluid was normal on several occasions. An electrocardiogram showed no conspicuous abnormalities. The total proteins of the blood at first as low as 4.6 gm.%, rose promptly to normal levels with a higher protein intake. On admission the phenolsulphonephthalein excretion was 65% in 2 hours. On the day before death this value had fallen to 22%.

Discussion. The conspicuous abnormalities encountered in this individual were polyneuritis, disturbances of vision and hearing, hypertension with evidence from examination of the urine of renal disease, fever, tachycardia, edema, anemia with leukocytosis and eosinophilia, a positive Wassermann reaction and the systemic manifestations of a chronic wasting illness. Abdominal pain although present, was not striking.

Changes in the skin, usually of a hemorrhagic variety, have been observed in periarteritis nodosa. Lamb¹ refers to a case in which there was desquamation of the entire body typical of scarlet fever, without, however, any known preceding eruption. Howard² notes the incidence of urticaria and erythemata. Whether or not the eruption considered to be lichen planus was related to the primary disease in the present case, is, of course, problematical since no microscopic examination of the skin was made.

Polyneuritis is too frequently encountered to merit further attention. There has been ample discussion concerning the mechanism whereby changes in the peripheral nerves are produced. Evidence has been offered which indicates that the nerves may be affected either by local circulatory disturbances or else by the action of toxins in the presence of an intact blood supply.³

Fever, so conspicuous a symptom here, is almost invariably present at some stage in the evolution of periarteritis nodosa. Arkin⁴ has more or less arbitrarily divided the course of the disease into four stages. During the first two of these: the degenerative and the acute inflammatory, fever is usual. When the processes of repair and granulation set in, the patient is afebrile. Tachycardia, likewise, is met with almost constantly.

In 34 cases reviewed by Lamb,¹ edema was observed in 61%. In the instance of the patient under discussion, anasarca, at first thought referable to reduced total blood proteins, persisted after these had been restored to a normal level.

It is reasonable to assume that syphilis had no etiologic relationship to the patient's main illness. The early course of the disease transpired during a period of persistent antiluetic therapy. Although cases of periarteritis nodosa associated with a positive Wassermann reaction have been recorded, the incidence of such is no higher than in any other group of individuals. In a case reported by Gray,⁵ the lesions of syphilis and periarteritis nodosa were exhibited side by side. The aorta as well as the small cerebral arteries showed characteristic luetic changes of considerable duration; while the arteries of the heart, liver, kidneys, adrenals, pancreas and lungs contained fresher lesions of a different sort, which were typical of periarteritis nodosa.

No organ is involved in this disease more frequently than the kidney. In 75% of 108 cases analyzed by Gruber⁶ renal changes were encountered. As a consequence, therefore, abnormal urinary constituents are the rule. Keegan⁷ had the opportunity to watch the progression of a vascular nephritis in a patient upon whom a nephrectomy had been performed 2 months before the illness terminated in uremia. Changes in the kidney removed at operation corresponded to an acute periarteritis nodosa, whereas those in the companion kidney at autopsy, indicated a vascular nephritis. From these observations Keegan concluded that certain instances of chronic arteriolosclerotic nephritis may be the sequelæ of an original periarteritis nodosa.

There was a mild secondary anemia with leukocytosis in the present case. In the more chronic forms of the disease anemia may become striking while a leukocyte count as high as 66,000 has been recorded (Lamb). Under ordinary circumstances the leukocytes range between 15,000 and 30,000.

Eosinophilia is encountered in less than 20% of the cases. In all likelihood the eosinophilia is a response to the destruction of the individual's tissues. Pathologically the same phenomenon is seen when there is infiltration about the diseased arteries by eosinophils. Certain cases have shown excessively high eosinophil counts up to 79% (Strong,⁸ Curtis and Coffey⁹). The eosinophilia has aroused the suspicion of a parasitic etiology of periarteritis nodosa especially because of the fact that a disease caused by parasites, bearing certain resemblances to it, occurs in horses and dogs. In the human disease, however, parasites have never been identified.

Hypertension has been recorded in the majority of instances where the blood pressure was measured. Thus, the blood pressure was elevated in 5 out of 8 children with periarteritis nodosa included in the series collected by Rothstein and Welt;¹⁰ while similar findings were encountered in 6 out of 7 of Strong's group. In our patient there were wide oscillations of the blood pressure, a phenomenon which appears to be of some diagnostic worth, for it was this observation which first suggested the diagnosis of periarteritis nodosa.

Over 4 years before, a man who at autopsy was found to have suffered from this disease died at this hospital. His clinical course had been most puzzling so that no satisfactory conclusions concerning the diagnosis were reached during life. It was a recollection of certain features of this man's illness that led to the first suspicion of the underlying disease in the present case. For this reason the history of the earlier case will be briefly reviewed.

CASE 2.—L. M., a Louisiana lumberman of 56 (Unit No. 22019), was admitted to the hospital on December 1, 1928. In the spring of 1927 he had had mumps with testicular involvement. A year later he was treated for prostatitis. In August, 1928, a fever of obscure origin appeared and it was for this reason that he was finally admitted to the hospital. At that time the important physical findings were: loss of weight, slow mental responses, intention tremor of the hands with fibrillary twitchings, hyperactive reflexes and weakness of the extensors of the left foot. At first there was slight improvement although he continued to run a low grade fever. However, in January, 1929, a new group of findings appeared with nausea, vomiting and abdominal distention, increasing drowsiness, wandering delirium, increased rigidity of the peripheral vessels, rapidly progressive retinal arteriosclerosis with hemorrhagic retinitis and extensive exudates ending in almost total blindness, leukocytosis up to 26,700, anemia, and albuminuria. After developing pneumonia, he died on April 8, 1929. Blood pressure on admission was 150/85 mm. This soon dropped to 118/90 mm. but once again started to increase. Late in January it was 168/84 mm.: a month later 205/110 mm. Subsequently a level of 220/125 mm. was attained. At autopsy, the spleen was found to be enlarged. There were small nodules along the cerebral arteries. Microscopically, were encountered characteristic lesions of periarteritis nodosa involving the arteries of the heart, pancreas, brain, kidneys and muscles.

It was the similarity between the rapid progression of hypertension in the 2 cases, with initial elevation of pressure followed by a temporary decline and once again steady increase, that first called to mind the possibility of periarteritis nodosa explaining the symptoms of the recent case.

More detailed mention of ocular symptoms will be made, since they provided such a dramatic incident in the course of the disease in the patient under discussion. Visual disturbances were noted in 3 of the cases analyzed by Lamb. The first individual reported by Bennett and Levine¹¹ suffered progressive loss of vision which was compatible with the advanced vascular retinitis which existed. The young girl studied by Goldstein and Wexler¹² provided no clinical evidence of visual affliction. Pathologically, however, ocular arterial changes were discovered confined to the choroidal vessels. Friedenwald and Rones¹³ examined the eyes from Case 2 with similar results. Here, likewise, inflammatory changes of periarteritis nodosa were limited to the ciliary and choroidal vessels while the retina showed extreme arteriolar sclerosis and albuminuric retinitis. These authors speculate as to the relation between the two types of vascular changes but conclude that final judgment must be suspended. Certain it is, nevertheless, that albuminuric

retinitis appears in the absence of periarteritic involvement of the retinal arteries. In support of the thesis that periarteritis nodosa is an allergic response to various infections, Helpert and Trubek¹⁴ offer the instance of a man who succumbed to a gonococcal endocarditis and subacute glomerular nephritis, who in addition was found to have isolated lesions suggestive of periarteritis nodosa in the arteries of the testis and choroid. Here, again, the retinal vessels were entirely uninvolved. In Case 1 there was occlusion of a central retinal artery while the smaller retinal vessels showed only minimal constriction in caliber. No other example of thrombosis of the central retinal artery in periarteritis nodosa has been reported and only a single author, Müller,¹⁵ has described retinal vascular changes of any sort.

Deafness in periarteritis nodosa is uncommon. Aside from Case 1, no mention of this symptom has been encountered. Druss and Maybaum¹⁶ discovered acute periarteritic changes in arteries of the temporal bone of a patient dying of the disease. In addition, there were several patches of otosclerosis unassociated with any vascular abnormalities. Clinically there had been no gross disturbance of hearing. In our case the otitic involvement was of the nerve type. One can only surmise that the auditory nerves may be attacked in periarteritis nodosa in a similar manner to the peripheral nerves.

Admittedly periarteritis nodosa is a rare disease. The clinical files of this hospital disclosed in addition to the 2 cases already recalled, only 1 other example of the condition.

CASE 3.—J. M. (Medical No. 54035) admitted to this hospital September 10, 1925, was a man of 23 upon whom an exploratory laparotomy was performed after several weeks of an illness characterized by fever, abdominal pain and eosinophilia. At operation small yellowish nodules along the gastric vessels and over the surfaces of the liver and spleen were disclosed. Microscopic examination proved the lesions to be periarteritic nodules.

It has repeatedly been suggested that the rarity of the ailment is partly attributable to the obvious difficulties in diagnosis. While this argument may have some clinical validity, it is unlikely that at autopsy the microscopic examination would fail to reveal the unmistakable characteristics of periarteritis nodosa. Nevertheless, 4 more instances of the disease were brought to light after a search through the pathologic records of over 13,000 autopsies. All 4 of these had, during life, masqueraded under the guise of cardiovascular renal disease; 2 dying in uremia, 1 of a cerebral hemorrhage, and 1 succumbing to myocardial failure. In only 2 cases had the pathologist ventured a suggestion of periarteritis nodosa, but a review of the sections with this disease in mind, left little doubt that all 4 represented this condition.

One other factor should be mentioned in relation to the infrequency of diagnosis of periarteritis nodosa, namely, that in a small

group of individuals the disease is not fatal. According to the statistics of Gruber⁶ from 10 to 12% of the cases recover. This opinion is borne out by evidence offered by certain of the fatal cases, wherein old healed lesions in some of the viscera may be found in a person dying of involvement of a single organ in which the disease was progressive. For example, Arkin⁴ records the instance of an individual whose death was attributable to cardiac and renal failure, while scarred areas produced by old periarteritic lesions were present in various other organs. It is conceivable that under certain circumstances all the lesions may heal so that for all practical purposes the patient is well, without the disease at the basis of his trouble ever having been recognized.

Conclusions. A fatal case of periarteritis nodosa without peripheral nodules, suspected and proved by biopsy antemortem, is recorded. The patient's illness was characterized by weakness, emaciation, fever, peripheral neuritis, abdominal pain, edema, occlusion of a central retinal artery, deafness, vacillating hypertension, tachycardia, anemia with leukocytosis and eosinophilia, and changes in the urine. The Wassermann reaction was positive. Potassium iodid failed to arrest the progressive course of the disease.

Mention is made of 6 other cases of periarteritis nodosa in the files of this hospital. One of these was diagnosed at autopsy; a second at laparotomy. The last 4 were recognized by searching through the autopsy material of the department of pathology.

The significance of some of the symptoms and signs encountered in periarteritis nodosa is appraised. Reasons are offered to indicate that the disease may not be quite as uncommon as the paucity of recognized cases would lead one to believe.

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THE MECHANISM OF DECREASE OF GASTRIC SECRETION WITH ADVANCING YEARS.

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WHILE it has been known for a long time that gastric anacidity occurs much more frequently in old than in young people,¹ Bloomfield and Keefer,² in 1928, were the first to demonstrate the steady drop in acidity which takes place with advancing years. Pollard and Bloomfield³ subsequently confirmed this finding with carefully standardized histamin tests on essentially normal people. Vanzant and her colleagues,⁴ analyzing a large mass of material, showed in addition that there was a difference between the two sexes, men on the whole having a more highly acid gastric juice than women. Finally the definitive studies of Pollard⁵ using histamin took into account not only age and sex but volume of secretion as well as acidity. The upshot of all this work is that the following points are established.

1. There is a marked fall in average gastric acidity of men with advancing years and the curve is a straight line.
2. The average gastric acidity of young women is distinctly lower than that of young men, but the fall with advancing years is very slight.
3. The average volume of secretion both of men and of women falls markedly with advancing years, and the curve is a straight line.

These phenomena could be explained theoretically in various ways. First, the average fall in acidity and volume of secretion with advancing years might be due to a gradual decline in each individual. On the other hand, it is conceivable that some people maintain their level of secretion unchanged throughout life whereas others suffer a very marked diminution; the curves based on average values could be the result of these two forces. And finally there

might be combinations of the two extremes. To settle this question it is necessary to measure the gastric secretion of the same series of people over intervals of years to find out what happens in the individual; the present observations represent a partial attempt to solve the problem along these lines. One can predict however on the basis of established data that the general defection of secretion with advancing years will not turn out to be due to a gradual fall in all people, because even in the older age periods a number of individuals are found who preserve a maximal secretion. Inasmuch as this secretion is still maximal it is clear that there can have been no drop from an earlier higher level. Detailed figures on this point may be found in Polland's paper.⁵

The rapidly increasing incidence of anacidity with advancing years also seems out of accord with gradual drop in secretion of the whole population.

Methods. Our plan was to repeat after a long interval the standard histamin test⁶ on a series of individuals under as nearly identical conditions as possible. While we had many original observations, it was surprisingly difficult to arrange for the repetitions after a period of 5 or more years. Some of the subjects could not be located, others were unable or unwilling to return and still others presented themselves but declined to have the test. Consequently we have only 6 observations, but the information yielded seems of value.

All the tests were carried out by the same observer under as nearly constant conditions as possible. On both occasions the patient was in bed in the hospital overnight and conditions were as nearly basal as possible. Exactly the same dose of histamin was given.

In order to interpret the tests repeated after long intervals the error inherent in the method, that is to say, the amount of variation to be expected between tests done at brief intervals, must be known. We have many observations which show that if the examinations are made under standard conditions on normal people practically identical results are obtained after intervals of a few weeks or a few months. The following example will suffice:

E. M., a healthy physician, aged 28, was examined on November 1, 1928, and again on December 6, 1928. The tests are shown in Table 1. The results agree closely. The volume of juice is slightly greater on the first test and the acidity is slightly higher on the second test. In neither case is the variation over 10%, an experimental error which could hardly be lower with a method of this sort.

When the histamin test is repeated immediately or within a few days the second examination may yield slightly higher values both for volume and acidity.⁷ The exact explanation is not clear.

RESULTS. The results of the histamin test repeated after intervals of 5 years or more in 6 subjects are shown in the following protocols (Tables 2 to 7).

TABLE 1.—HISTAMIN TEST REPEATED AFTER INTERVAL OF A FEW WEEKS ON A NORMAL MAN.

November 1, 1928.

10-minute period number.	Volume of secretion per 10-minute period (cc.).	Free HCl.	Total acid.
		Histamin 0.6 mg.	
1	47	70	78
2	48	88	96
3	43	98	106
4	42	84	92
5	28	84	93
	<hr/>		
Total	208		

December 6, 1928.

Histamin 0.6 mg.				
1	42	70		79
2	45	84		94
3	44	95		102
4	35	105		114
5	25	102		112
Total	191			

TABLE 2.—HISTAMIN TESTS DONE NOVEMBER 11, 1927, AND JANUARY 17, 1935. INTERVAL 7 YEARS. (Case 18. Male, aged 42—Neurosis.)

10-minute period number.	Volume of secretion per 10-minute period		Free HCl.		Total acid.	
	(cc.).		Test 1.	Test 2.	Test 1.	Test 2.
	Test 1.	Test 2.				
			Histamin 0.8 mg.			
1	21	15.5	96	74	110	92
2	25	20.5	132	120	138	136
3	28	24	144	123	150	139
4	25	18.5	138	120	145	135
5	18	15	138	115	144	128
Total	117 cc.	93.5 cc.				

Comment. Here there was a moderate but definite drop in the total volume of secretion amounting to 20%. The highest 10-minute volumes on first and second tests were 28 cc. and 24 cc. Acidity on the second test was slightly less than on the first, but hardly more than can be accounted for by experimental variation.

CONCLUSION. Definite decrease in amount of secretion; slight (?) decrease in acidity.

TABLE 3.—HISTAMIN TESTS DONE APRIL 12, 1928, AND FEBRUARY 9, 1934. INTERVAL NEARLY 6 YEARS. (Case 44. Male, aged 20—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
	Histamin 0.5 mg.					
1	16	31	65	95	77	105
2	20	35	100	108	110	120
3	26	33	135	112	145	122
4	16	26	130	116	140	126
5	10	14	118	96	125	102
Total	88 cc.	139 cc.				

Comment. This case is of interest since the volume of secretion was definitely higher on the second test both as to total quantity in 50 minutes and as to greatest amount in a 10-minute period. The acidity on the other hand was distinctly lower.

TABLE 4.—HISTAMIN TESTS DONE MAY 14, 1928, AND SEPTEMBER 28, 1933.
INTERVAL $5\frac{1}{2}$ YEARS. (Case 46. Male, aged 27—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
Histamin 0.6 mg.						
1	10	15	85	116	98	131
2	39	36	114	134	120	144
3	32	40	126	140	136	151
4	29	35	128	136	138	150
5	24	24	128	138	132	150
Total	134 cc.	150 cc.				

Comment. The highest acidity attained after histamin was slightly higher in the second test. The difference is not definitely outside the limit of error. The total quantity of juice in 50 minutes is also slightly higher (a difference of 16%) although the highest volume for any one period was the same in the two tests (39 cc. and 40 cc.).

CONCLUSION. Very slight increase in gastric secretion (both volume and acid) on second test of doubtful significance.

TABLE 5.—HISTAMIN TESTS DONE OCTOBER 14, 1928, AND OCTOBER 5, 1933.
INTERVAL 5 YEARS. (Case 60. Male, aged 41—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
Histamin 0.5 mg.						
1	15.5	4	42	34	55	45
2	27	7	96	96	103	108
3	27	17	105	96	111	108
4	19	14	100	100	107	112
5	8	11	88	55	98	60
Total	96.5 cc.	53 cc.				

TABLE 6.—HISTAMIN TESTS DONE JANUARY 8, 1928, AND OCTOBER 26, 1933.
INTERVAL NEARLY 5 YEARS. (Case 74. Male, aged 39—Duodenal Ulcer.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
Histamin 0.65 mg.						
1	83	55	76	108	84	115
2	84	82	122	116	130	128
3	74	74	140	127	146	138
4	55	63	128	118	134	129
5	53	48	124	106	132	118
Total	348 cc.	322 cc.				

Comment. The acidity was practically identical on the two tests, the highest values being 111 and 112. There was, however, a

marked drop in volume of secretion in the second test amounting to 46%.

CONCLUSION. Marked drop in volume of secretion without change in acidity.

Comment. This case is of special interest since the patient had the highest volume of gastric secretion we have ever encountered in many hundreds of tests. The results both as to acid and volume are practically identical on the two tests. The slightly lower figures on the second test are well within limit of error.

TABLE 7.—HISTAMIN TESTS DONE SEPTEMBER 20, 1927, AND SEPTEMBER 21, 1933. INTERVAL 6 YEARS. (Case 8. Male, aged 45—No Disease.)

10-minute period number.	Volume of secretion per 10-minute period (cc.).		Free HCl.		Total acid.	
	Test 1.	Test 2.	Test 1.	Test 2.	Test 1.	Test 2.
	Histamin 0.8 mg.					
1	17.5	14	56	42	74	54
2	24	19	84	75	90	94
3	25	23	88	92	96	112
4	25.5	22	96	104	106	120
5	23.5	19	102	97	114	116
6	18	12	88	94	100	112
Total	133.5 cc.	109 cc.				

Comment. The highest acidity after histamin in both tests was practically the same, the difference between 114 and 120 being within the limits of error. The volume of secretion in an hour is definitely less on the second test (a decrease of 18%), although the maximum output in a 10-minute period is practically the same (25.5 cc. and 23 cc.).

The striking fact revealed by these protocols is the slight differences in secretion between first and second tests. In all of our work on normal standards and comparative values for secretion in different people we have taken the highest acidity reached at any time during the test and the largest volume of secretion for any one 10-minute period as indicating the supreme secretory ability of that particular stomach under standard conditions of stimulation. These values, taken from the present series, are herewith tabulated (Table 8).

TABLE 8.—HIGHEST ACIDITY AND VOLUMES OBTAINED IN 6 CASES.

Case No.	Highest total acidity attained during		Difference.	Highest 10-minute volume of secretion (cc.) in		Difference.
	Test 1.	Test 2.		Test 1.	Test 2.	
18	150	139	-11	28	24	-4
44	145	126	-19	26	35	+9
46	138	151	+13	39	40	+1
60	111	112	+1	27	17	-10
74	146	138	-8	84	82	-2
8	114	120	+6	25.5	23	-1.5
Average	134	131	-3	38	36	-2

By these criteria no significant difference is made out between the first and second sets of tests, although there is perhaps a slight

tendency to lessening of acidity and volume. One must look elsewhere, then, for the explanation of the general fact that gastric secretion decreases with advancing years. The answer we believe lies in certain cases in which there is a very rapid deterioration of secretion and we are able to report 2 instances of this sort.

Case Abstracts. CASE 1.—R. N. (No. 162263), a 33-year-old teamster, was first seen in 1927 with the complaint of abdominal pain. Roentgen-ray showed a penetrating ulcer on the lesser curvature of the stomach. On April 19, 1927, even with the weak stimulus of an Ewald meal the free HCl was 48 and the total acid was 61. These findings were confirmed with an alcohol test meal. In June, 1927, he felt better after Sippy treatment, but Roentgen ray still showed the ulcer crater. He disappeared until November, 1934, when he returned with complaint of poor appetite and vomiting for a year. Roentgen ray no longer showed ulcer but the histamin test yielded *no free HCl*. He had used alcohol freely and the question of gastritis as a cause for the disappearance of acid was raised.

CASE 2.—J. D. (No. 187818), a 57-year-old photographer, was first seen in 1929 complaining of abdominal discomfort. Roentgen rays showed a penetrating gastric ulcer with pyloric obstruction. Histamin test on May 5, 1929, showed *free HCl* 88, *total* 98, highest volume per 10-minute period 41 cc. The ulcer was excised and a gastro-enterostomy was done. No large area of stomach was removed, the specimen being only a little over 1 cm. in diameter. It showed a benign gastric ulcer. On December 17, 1929, patient was well and a second histamin test showed *free HCl* 34 and *total* 44. He returned in September, 1933, with no stomach complaints but with intermittent claudication. Histamin test September 9, 1933, showed *free HCl* 0 and *total* 12, with maximum 10-minute volume 17 cc. The test was satisfactory and there was no regurgitation of bile into the stomach.

While these 2 patients were not really normal, they illustrate the fact that rapid deterioration of gastric secretion may actually take place.

Discussion. These observations show that there is no uniform steady decline of gastric secretion in all people with advancing years. In some the level of secretion remains essentially unchanged over long periods, in certain people there is a slight drop or even a slight increase and in still others a rapid failure of secretion leads to gastric anacidity. The results of these various influences gives the smooth curve of average deterioration. So far it has not been possible to correlate the course of events in the individual with any special clinical phenomena.

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CARCINOMA OF THE BREAST IN ONE OF HOMOLOGOUS TWIN SISTERS.

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WHETHER all malignancies in twins occur simultaneously in both is still a moot question. Bauer's¹ theory is that the constitutional tendency to cancer is based on the effect of predisposing genetic factors, and if this is correct, he states, then unicellular twins—that is, individuals of identical constitution, for they have grown from the same impregnated ovum—must both suffer from tumor or cancer, with great frequency.

According to McFarland and Meade,² since homologous twins arise from a single egg and consist of approximately equal quantities of material normally destined to produce a single individual, but which through some circumstances of early separation, produced two individuals, they closely resemble each other in every particular. These authors state there are no reported cases in which one homologous twin suffered from a tumor without its fellow being similarly affected. So that if one twin has cancer the other twin must necessarily have cancer too. Moreover, McFarland and Meade state such tumors occurring in homologous twins should be similar, symmetrical and simultaneous, and they quote a report of Burkhard's describing a case of cancer of the breast occurring in twin sisters at the same time.

Because of these statements, I consider it of interest to report a case that has been under my care during the past 2 years, where one twin sister had a cancer of the left breast, while the other had no evidence, either visible or palpable, of malignancy either in her breasts or elsewhere. This is the first case of malignancy in twins I have personally had to take care of in my practice.

McFarland and Meade state that twin cancer observations require that both twins shall have lived long enough to develop the disease and shall have lived near enough together for each to know about the other and for each to be studied in comparison with the other by the same observer.

The twins under consideration have lived together all their lives, 53 years, both are unmarried, both seemingly have a similar form and structure, act in similar manner in their daily habits. Both have for many years been under medical observation and under my care since January, 1933, a period of over 2 years. On February 11, 1935, the twin not affected by cancer was again carefully examined by me and no cancerous development discovered during a period of 2 years under my observation. McFarland states in a

personal communication that one should observe these cases for several years. More than 2 years should have shown malignant development in the second twin if it were destined to appear. A report of the other twin follows:*

Case Abstract. N. S., single, aged 51, was referred to me by the late Dr. Phil Graussman on January 20, 1933, for irradiation following a radical mastectomy for left breast malignancy, first noted in September, 1932, and operation performed the following month. The patient had always been well except for occasional colds, and an appendectomy in 1922. Her menstrual history was normal and without noticeable effect on her breasts; she had never been married. She and her sister dressed and acted alike and enjoyed the same kind of social and recreational activities.

In September, 1932, the patient noticed a lump in the upper quadrant of her left breast and went to her physician who advised immediate operation. Radical removal of the breast was carried out during the first week in October. The pathologic examination of the tumor showed it to be adenocarcinoma. Following an uneventful recovery from the operation, she was referred to me for postoperative irradiation. The twin sister examined at this time, showed no abnormalities except moderate deafness which had followed an attack of scarlet fever in childhood. This twin is somewhat stouter than the sister with cancer. Both sisters have wartlike papillomata on the neck.

The patient remained well until September, 1934, when a small recurrence at the site of the previous operation scar on the left breast was noted. A local resection of the recurrent malignant tissue was carried out and the patient referred for further Roentgen ray therapy. Because of the possibility of malignancy occurring in both twins, as suggested by McFarland and Meade, both sisters were again examined by me on February 11, 1935. They were found to be in good general condition, although both were simultaneously going through early evidences of menopause change. The patient whose breast had been removed showed no visible or palpable evidence of recurrence or extension of the malignant process and gave no symptoms of its presence anywhere in the body. The examination of the other sister gave no evidence whatsoever indicating the presence of cancer in her breasts or elsewhere.

It appears that here is a case which obviously is contradictory to the definite pronouncement by McFarland and Meade, and by Bauer, that cancer in homologous twins must necessarily be simultaneous. More than 2 years have elapsed since cancer appeared in the one sister, a sufficient time for cancer to have developed in her twin if it were to occur at all. The twins will be observed from time to time and any appearance of malignancy in the second twin will be reported.

* Since writing this paper the twins were again seen by me on May 29, 1935, and the second twin is still without signs of malignancy.

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CHOKED DISC IN SYPHILIS OF THE NERVOUS SYSTEM.

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THE neurologist, confronted with the signs and symptoms of increased intracranial pressure and choked discs, must always give precedence to brain tumor as being the most likely possibility. Experience has shown convincingly that, though there are of course other causes, tumor is far and away the most common reason for increased pressure within the skull. One cannot emphasize too strongly, therefore, the necessity for giving it the weightiest consideration in determining the cause of choked disc and of increased intracranial pressure.

There are other causes of choked disc, however, and among the less frequent of these is syphilis of the nervous system. Recent experience with 5 cases of central nervous system syphilis has convinced us that choked disc may occur in the course of the disease, that it may disappear completely during the course of antisypilitic treatment, and with it other signs of increased intracranial pressure. That syphilis of the nervous system may be present with brain tumor is well known, for among 22 meningeal fibroblastomas of the frontal lobes, Frazier and Alpers¹ found 3 with serologic evidence of central nervous system syphilis.

We attach little significance to positive serologic reactions in suspected cases of brain tumor. We agree with Frazier, who in a differentiation of frontal lobe fibroblastoma and syphilis, says, "In 3 of our cases serologic tests were positive, one with 20 cells and a colloidal gold curve of 554443210 in the spinal fluid. But in all 3 cases there were signs of increased intracranial pressure with papilledema of 2, 3.5 and 5 diopters. We realized, of course, that papilledema was not inconsistent with a diagnosis of syphilis, but the other signs of tumor were sufficiently outstanding to outweigh the positive serologic reactions. As a fact, it has been our practice to attach little importance to positive Wassermann reactions, either of the blood or of the spinal fluid, in persons thought to have tumors of the brain, *except when the signs of tumor are vague.* (Italics ours.) When there is indisputable evidence of a mass lesion, even though serologic tests are positive, an exploratory operation is indicated. In attaching little importance to positive serologic reports

we have been influenced in part by our experience of 30 odd years in the Neurosurgical Clinic of the University Hospital, during which time only 1 gumma has been exposed on the operating table."

This had always been our view, and is in fact the view we hold today. That syphilis of the nervous system may of itself cause choked disc has been abundantly demonstrated to us, however, in the following 5 cases which we have studied in the past year. Its differentiation from tumor will be considered subsequently.

Report of Cases. CASE 1.—*Severe headaches, diminution of vision, loss of hearing in left ear. Bilateral choked discs, partial left oculomotor weakness, deafness left ear. Blood and spinal fluid strongly positive. Complete recession of subjective symptoms and choked disc under antisyphilitic treatment.*

M. B. (D 1246) a colored woman, aged 32, was admitted to the Philadelphia General Hospital, January 26, 1934. She complained of pain in the shoulders and deafness in the left ear. She had been well until September, 1933, about 4 months before admission, when she contracted a severe head cold with much nasal discharge and profuse lachrymation. This cold lasted for 4 weeks, despite treatment. It was followed immediately by a severe constant frontal headache described as a deep, boring pain over the eyes. The headache was so severe that she was forced to give up her work; often it aroused her during the night. It lasted for 1 month and disappeared spontaneously. Shortly after this her right shoulder began to ache severely followed 1 month later by severe pain in the left shoulder. About a month before admission to the hospital she noticed that her vision was becoming dim and at times she saw double. Simultaneously, she began to develop deafness in the left ear. This progressed up to the time of admission. The only significant features in her past history were 3 children stillborn at term and the loss of 20 pounds in weight since the onset of her illness.

Examination was negative except for the neurologic features. When first examined, January 29, 1934, she had sluggish and unequal pupils, the left being the larger. The left palpebral fissure was slightly smaller and there was questionable impairment of downward movement of the left eyeball. There was decreased air conduction in the left ear. The right corner of the mouth drooped slightly at rest, but moved well on voluntary innervation.

When examined 5 days later the condition gave evidence of having progressed in the meantime. There was now a decided ptosis of the left eyelid, weakness of the left superior rectus, more marked deafness of the left ear and bilateral weakness of the soft palate. The tendon reflexes were slightly more active on the right side but there were no findings otherwise in the extremities.

Laboratory Studies. The blood Wassermann reaction was 4+. Spinal fluid (January 29, 1934) showed a pressure of 22 mm. of mercury, 87 lymphocytes, a trace of globulin, a 4+ Wassermann, and a gold sol. of 4544444321. A later spinal fluid (February 19, 1934) contained 35 lymphocytes.

The urine was normal in all respects. The blood sugar was 124; blood urea 14; red blood cell count 4,200,000; hemoglobin 85%; leukocyte count 5400 and 63% lymphocytes.

Bárány examination revealed no evidence of a cerebellopontile lesion and pointed to a supratentorial lesion.

Roentgen ray of the skull revealed no signs of increased intracranial pressure. The sella turcica was normal.

Eyc Examinations. The eyes on admission (February 1, 1934) showed a choking of 5 diopters in each eye. Thirteen days later (February 14, 1934)

after antisyphilitic treatment had been under way, there were 2 diopters of swelling in the right eye and 4 in the left. One week later (February 21, 1934) shortly before discharge, there was no swelling in either eye.

Course. The patient was given intensive antisyphilitic treatment. She received 20 inunctions of mercury, 4 injections of bismuth intramuscularly and ascending doses of potassium iodid by mouth. She showed almost immediate subjective improvement. Her hearing increased and shortly before discharge became practically normal. The pain in the shoulders and neck disappeared. She left the hospital against advice free of her symptoms and neurologic signs.

The following case illustrates the need for surgical intervention in patients who do not respond to antisyphilitic treatment alone.

CASE 2.—Severe frontal headaches and progressive loss of vision for 6 months. Progressive loss of hearing for 2 months. Bilateral choked disc. Roentgen ray evidence of left parasellar lesion. Arachnoiditis of optic chiasm exposed at operation. Recovery.

J. G., a colored man, aged 44, was admitted to the Graduate Hospital, August 17, 1933, complaining of headache and failing vision. He had had severe, constant frontal headache for 6 months, and these were becoming progressively more intense. At times he had spells of complete loss of vision which lasted a few minutes. His vision had become worse in the 6 months before his admission to the hospital. Two months before entrance he developed ringing in his left ear and progressive loss of hearing on this side.

Examinations revealed cardiac enlargement with a blood pressure of 170/90 and generalized arteriosclerosis.

Neurologic examination showed anosmia on the left side, round, equal pupils reacting well to light and accommodation, papilledema of 2 diopters in each eye, a slight weakness of the left lower face, tremors of the fingers and a generalized hyperreflexia. There was some concentric contraction of the left visual field; the right was normal.

Laboratory Studies. The blood Wassermann reaction was strongly positive. The spinal fluid was under 22 mm. of mercury pressure. It contained 2 cells and a slight increase in protein and the Wassermann reaction was positive.

The blood count and blood chemistry were normal.

The urine contained a trace of albumin. There was 60% excretion of phenolsulphonephthalein in 2 hours.

Roentgen ray of the skull showed deformity of the sella turcica by stereoscopic views. The dorsum sellæ and posterior clinoid process on the left side were almost completely eroded. On the right side only a remnant of the posterior clinoid and dorsum sellæ remained. The signs pointed to a parasellar lesion on the left side.

Course. A course of antisyphilitic treatment consisting of mercury, iodids, bismuth and bismuth arsphenamin sulphonate was given without results, so that it was decided to explore the suprasellar and parasellar regions.

Operation. On September 21, 1933, Dr. F. C. Grant reflected a left frontotemporal bone flap. The left optic nerve was found to be covered by a heavy white membrane. This thickened arachnoid was found to extend across the anterior portion of the optic chiasm to involve the right optic nerve. This tissue was removed by blunt dissection and both nerves and chiasm freed. There was no evidence of tumor.

Recovery from the operation was uneventful. The headache disappeared

completely. Examination of the eyes (October 20, 1933) about 4 weeks after operation, revealed no choked disc.

Examination about 13 months after discharge (November 8, 1934) revealed no headache, or subjective symptoms of any sort. Examination showed only a slight weakness of the lower part of the right face.

Cases which do not respond to ordinary antisyphilitic remedies must be treated by more drastic means such as fever therapy. This is illustrated in the case which follows:

CASE 3.—Oral syphilis 1 year previous to admission. Frontal headaches, diplopia, visual loss for 6 weeks. Bilateral choked disc, weakness right internal rectus, contraction of visual fields. Serologic evidence of central nervous system syphilis. Antisyphilitic treatment with marked improvement.

R. S., a girl, aged 20, was admitted to the Graduate Hospital on September 7, 1934. About 1 year before admission, she had had some sores in her mouth and was treated by injections into her arms and buttocks. The sores cleared up promptly. Following this she was in good health until about 6 weeks ago, when she began suddenly to complain of frontal headaches. These were chiefly frontal but radiated also to the temporal, parietal and occipital regions. They were so severe that she was forced to give up work. At the same time she experienced photophobia, diplopia and marked disturbances of vision. She had a number of spells of numbness in the right hand during which she became momentarily speechless, but she had never suffered from spells of loss of consciousness.

Examination of her general physical being was entirely negative. Neurologic examination revealed pupils which were entirely normal in their reactions to light and accommodation. The visual fields were somewhat contracted. There was choking of 5 to 6 diopters in each eye with retinal exudates and hemorrhages. The right internal rectus was somewhat weak. Otherwise the neurologic examination was entirely negative save for absent abdominal reflexes.

Laboratory Studies. The blood Wassermann reaction was positive by the Kahn test.

The spinal fluid was under a pressure of 22 mm. of mercury. It contained 107 cells, all lymphocytes and a marked increase in protein. The Wassermann reaction was negative. The colloidal gold test was 2211333211. The spinal fluid chlorids were 656 mg.

Urinalysis was normal.

Roentgen ray of the sinuses revealed moderate clouding of both frontals, haziness of some of the right ethmoid cells, marked clouding of the left maxillary sinus, and moderate clouding of both sphenoid sinuses.

The skull Roentgen ray revealed a normal sella turcica measuring 7 by 8 mm. There was no sign of increased intracranial pressure.

Course. There were no localizing signs of brain tumor and the case was considered to be one of syphilitic meningoencephalitis. Treatment was instituted immediately. She was given mercury inunctions daily together with 10 grains of sodium iodid daily. Her headache improved greatly after a week's treatment. Since her eyes showed no improvement it was decided to treat her more intensively. She was given injections of typhoid vaccine every other day. She had as a result of these treatments 10 severe febrile reactions, her temperature rising to between 103° and 105° F. On the days when she did not receive treatment she was given a mercury inunction. In addition she received iodobismitol (2 cc. intramuscularly) every 3 or 4 days, and 30 grains of sodium iodid by mouth daily.

Under this treatment her headache disappeared entirely and her vision improved markedly. She was discharged from the hospital in good condi-

tion. She still had slight weakness of the right internal rectus muscle but no diplopia. The visual acuity in the right eye was 6/15 and in the left eye 6/9. The choked disc had receded from 5 to 6 diopters to 1.5 diopters and the visual fields were definitely fuller. Subjectively she felt in very good condition.

CASE 4.—Memory impairment 8 or 9 months. Headache, diminution of vision, diplopia, transitory blindness for 3 months. Convulsive seizures 4 weeks. Bilateral choked disc, diminution of hearing in left ear, weakness left lower face, tremors left side, impairment of memory. Tertiary lesions on skin. Strongly positive blood and spinal fluid serology. Subjective improvement with antisyphilitic treatment.

B. B. (29928) a colored woman, aged 47, entered the University Hospital on October 3, 1934, on the Neurosurgical Service of Dr. C. H. Frazier. She had been transferred from the Pennsylvania Hospital where she was under the care of Dr. Thomas McCrae. She had had frequent spells of loss of memory for 8 or 9 months, during which time she had noted increasing difficulty in adjustment to her environment. For 3 months, she had noticed diminution of vision, diplopia, visual hallucinations and periods of transitory blindness. She could give no further information about these various symptoms. About 4 weeks before admission to the hospital, she fell and struck her head on the floor. She was unconscious for several hours but was able to return to work in a few days. After this she was forced to remain out of work from time to time because of illness. For 4 weeks she had suffered from seizures in which she suddenly developed coarse tremor of both hands, followed quickly by sudden twitching and falling, without loss of consciousness. She had had several seizures of this sort, each one lasting about 10 minutes. She gave a history of receiving injections in her buttocks and arm. She had had 6 illegitimate children, all of whom were born dead at term. She used alcohol freely.

Examination revealed a clover form lesion on her forehead and a deformity and ulceration of the left leg. These were considered to be tertiary lesions of syphilis by the dermatologic consultant. She had in addition a severe scar involving the soft palate and tonsillar fossæ, which might very well have been due to old syphilitic lesions. The liver was enlarged.

Neurologic examination was quite variable. When first seen in the Pennsylvania Hospital, she was very much clouded, and had severe headache. Several days later in the University Hospital, she had much less headache and was much less confused. She was still disoriented and her memory was very poor. The pupils were regular, and reacted well to light and accommodation. She had incomplete loss of hearing in the left ear, a suggestive left central facial weakness, coarse tremor of the tongue, slight tremor of the left arm, and absent abdominal reflexes. At times the facial weakness was much more evident than at others. The mental responses varied widely from time to time. On some occasions there seemed to be evidence of weakness of the right hand and arm; on others it was absent. Visual field studies revealed a bitemporal hemianopsia. There was 5 diopters of swelling in each eye. There were no other significant neurologic findings.

Laboratory Studies. The blood Wassermann reaction was strongly positive. The spinal fluid was under a pressure of 190 mm. of water. It contained 85 lymphocytes and 85 mg. of protein. The Wassermann reaction was strongly positive. The colloidal gold was 0012344410. The urine was negative. Roentgen ray of the skull revealed a sella turcica which measured 14 by 8 mm. There was a suggestion of atrophy of the dorsum sellæ. The findings were suggestive of increased intracranial pressure.

Course. During the patient's stay in the hospital of 28 days, she received 20 grains of potassium iodid 3 times daily, and 8 injections of mercury succinimid (gr. $\frac{1}{4}$) intramuscularly. She improved a great deal mentally.

She became quite oriented and clear, and was able to work about the ward. The headache disappeared completely. The choking receded to 2 diopters in the left eye.

The following case illustrates a gratifying response to intensive treatment with bismuth in the presence of long-continued choked disc without loss of visual acuity.

CASE 5.—Headache, photophobia, mental confusion and later euphoria. Increasing choked disc to 6 diopters despite antisyphilitic treatment. Disappearance of choked disc under intensive antisyphilitic therapy.

T. P. (30310), a colored woman, aged 40, entered the University Hospital under the care of Dr. C. H. Frazier, November 28, 1934. She was transferred from the Pennsylvania Hospital where she was under the care of Dr. A. G. Fewell. In the spring of 1934, she had been troubled with sore and painful eyes, photophobia and lachrymation. This subsided and in September, 1934, she developed a generalized headache, gradual loss of vision, and increasing pain in her eyes, for which she was admitted to the Pennsylvania Hospital. The headache became more severe and the eye symptoms persisted. She became more drowsy, confused and stuporous in the hospital. She developed nausea and vomiting in addition to her other symptoms. Examination in the Pennsylvania Hospital on November 4, 1934, revealed choked disc of 3 diopters. She had a slight right central facial weakness, decreased power in the right hand grip, and astereognosis of the right hand. The blood Wassermann reaction was strongly positive. The spinal fluid examination revealed 36 cells, chiefly lymphocytes, a negative Wassermann reaction and a colloidal gold curve of 0012321000. Antisyphilitic treatment was instituted and carried out for about 4 weeks but despite this the choked disc increased to 6 diopters.

Under antisyphilitic treatment from November 2, to November 28, in the Pennsylvania Hospital, the mental confusion and stupor gradually cleared until the patient became quite clear mentally. The headache disappeared completely and the iritis which she had on admission to the hospital became much better with daily installations of homatropin. Repeated neurologic examinations revealed only unequal, irregular pupils, the right larger than the left. The right pupil reacted very sluggishly to light; the left was extremely irregular and stiff to light. Despite the remarkable improvement in the headache and in her mental state, the choked disc increased and the visual acuity became less under antisyphilitic treatment. She was transferred, therefore, to a Neurosurgical Service because, while it was felt that her condition was due to syphilitic meningitis, the increasing choked disc and the decreasing visual acuity made it advisable to keep her under observation on a surgical service where steps could be taken to save her eyesight if necessary.

Upon transfer she was quite clear mentally; she had no headache nor photophobia. Her only neurologic signs were large, irregular, fixed pupils. The blood Wassermann reaction was moderately positive. She had 5 diopters of choking in each eye and a beginning bitemporal hemianopsia. The vision was 6/20 in each eye.

Treatment. As noted previously, she received weekly injections of both bismuth and mercury in addition to iodids by mouth for 4 weeks. Despite this her choked disc continued to progress and the vision became worse.

She was then placed on 4 injections of soluble bismuth each week together with 25 to 50 grains of potassium iodid 3 times daily. She continued on this treatment for 2 weeks. In 2 days her vision increased from 6/20 in each eye to 6/6 in the right eye and 6/12 in the left eye. The choking decreased from 5 to 4 diopters in 6 days. In 8 days it had decreased to 3 diopters in

each eye. In 13 days after this intensive treatment was started, the eye-grounds showed no choking. There was only a blurring of the nasal side of the discs. Three weeks after discharge the optic discs showed no swelling whatever.

Analysis of Symptoms and Signs. *Symptoms.* In all 5 cases severe frontal headache was a constant feature. It was a severe, constant, non-throbbing ache, often radiating to the temporal or even as in 1 case, to the occipital area. On the whole, however, it was closely confined to the frontal area. The severity of the headache simulated closely that usually encountered in brain tumor. Of all the symptoms it was by far the most disabling.

Just as constant was dimness of vision which was also present in all 5 instances. Usually it manifested itself early in the disease; almost as early as the headache, for example. Once present, it appeared to progress rapidly, so that at the time of admission to the hospital it usually constituted a serious symptom. Despite its prominence and seriousness in the clinical picture, it was not often associated with a very severe loss of visual acuity.

Progressive loss of hearing in one ear was present in 3 of the 5 cases. It was a distracting but not a serious symptom. In 1 instance it loomed so large in the patient's mind that suspicion was centered on the cerebellopontile angle as the seat of the disease.

These were the three most prominent symptoms. Diplopia was an occasional complaint. Convulsions were strikingly absent except in Case 4 where it is questionable whether true convulsive seizures were ever present. The attacks referred to in the history appeared to be rather in the nature of a severe, coarse, generalized tremor. Photophobia was present in a few instances.

Signs. The most constant sign was choked disc. This was as high as 5 diopters in 4 cases and 2 diopters in the fifth. There was nothing to differentiate the process from the type of swelling of the optic nerve head seen in increased intracranial pressure due to tumor. The retina in none of the cases revealed any evidence of inflammation, and in no case was there any sign of a neuroretinitis of the syphilitic type. There was the usual appearance of swelling and protrusion of the optic nerve head with later evidences of organization.

A recent analysis of 50 cases of acute syphilitic meningitis by Drake² reveals choked disc in 16. The swelling varied from 2 to 5 diopters. It was bilateral in 14 and unilateral in 2 cases.

Deafness was found in 2 instances. It was a prominent subjective complaint in 3 cases.

Incomplete oculomotor palsies as seen in a unilateral ptosis with partial inferior rectus weakness in 1 case, or an incomplete internal rectus weakness in another were occasionally disclosed. A complete external ophthalmoplegia either unilateral or bilateral was never found among our 5 cases.

Despite the undoubted serologic evidence of central nervous system syphilis, the pupils were surprisingly normal in all instances. The Argyll Robertson pupil was completely lacking in all instances; indeed not even evidences of a syphilitic pupil could be disclosed.

The visual fields were normal in 2 cases. In 2 patients a bitemporal hemianopsia was present; and in the fifth case, the visual fields were generally contracted.

In 3 cases there was a slight central facial weakness, but without signs of weakness in the limbs. Tremors of the limbs, involving either one limb or several members, was found in a few cases. In 2 cases there was severe mental confusion and disorientation.

Blood and Spinal Fluid Findings. The blood Wassermann test was positive in 4 cases. It was strongly positive in 2 cases and recorded merely as positive in 2 others. The fifth case was negative.

The spinal fluid cell count was high in 3 cases: 85, 87 and 107. In 1 case, it was 36 and in another was only 2. In the cases with pleocytosis all the cells were lymphocytes.

The spinal fluid Wassermann reaction was positive in 4 cases and negative in 1.

The colloidal gold reaction was of the paretic type in 1 case and showed deviations from the normal in the other 4.

In 4 cases the spinal fluid pressure was high, 22 mm. Hg. In the other case it was about the border-line of high normal, 190 mm. of water.

The Problem of Diagnosis. The question of greatest importance, of course, is that of diagnosis. Given choked disc in a patient, how are we to determine that it is due to central nervous system syphilis and not to brain tumor? The first criterion of importance is the absence of localizing signs and the variability of those signs present. The absence of focal signs is not in itself important because there are all too many tumors which give no evidence of their location by focal signs. Taken with the other criteria however, this has some practical importance. Even more significant however, is the variability of those signs which are present. These seem to change from one examination to another. Patients who present one set of signs one day either do not exhibit these signs on subsequent examination or present totally different signs. So variable may these signs be that the question may arise whether the findings observed were really present.

Another factor of importance in diagnosis is the serology. The blood Wassermann test is always positive. There is nearly always an increase in the spinal fluid cell count, the cells being chiefly lymphocytes. There may, however, be no increase in cells as for example in Case 2, in which the meningeal reaction was so chronic that no cell rise was observed. The spinal fluid Wassermann test is usually positive but may be negative as in Case 3. The colloidal gold curve shows deviations from the normal. In the evaluation

TABLE 1.—ANALYSIS OF DATA.

Case.	Age (yrs.).	Symptoms.	Signs.	Choked disc.	Blood Wassermann reaction.	Spinal fluid.			
						Pressure.	Cells.	Wassermann reaction.	Gold sol.
1	32	Frontal headache Dimness of vision Deafness left ear	Prompt pupillary reaction to light Left pupil larger Ptosis left upper lid Deafness left ear Weakness soft palate Weakness left lower face	O.D. - 5 D. O.S. - 5 D	Strongly positive	22 mm. Hg	87	Strongly positive	4544444321
2	44	Frontal headache Failing vision Deafness left ear	Anosmia—left Regular pupils, reacting well Weakness left lower face Tremors of fingers. Hyperreflexia	O.D. - 2 D O.S. - 2 D	Strongly positive	22 mm. Hg	2	Positive	
3	20	Frontal headaches Diplopia Dimness of vision Sensory Jacksonian fits Transitory aphasia	Regular pupils, reacting well Contracted visual fields Weakness right internal rectus	O.D. - 5-6 D O.S. - 5-6 D	Positive	22 mm. Hg	107	Negative	2211333211
4	47	Memory loss Dimness of vision Visual hallucinations Epileptiform seizures	Confusion and disorientation Regular pupils reacting well Loss of hearing in left ear Tremor of tongue and left arm Bitemporal hemianopsia	O.D. - 5 D O.S. - 5 D	Strongly positive	190 mm. H ₂ O	85	Strongly positive	0012344410
5	40	Sore eyes Lachrymation Headache Loss of vision Mental confusion	Unequal, irregular pupils, right larger than left Slight right central facial weakness Slight weakness right hand, disappearing under observation Bitemporal hemianopsia	O.D. - 5-6 O.S.	Positive	30 mm. Hg	36	Negative	0012321000

of the spinal fluid signs one may say that in a suspected case of syphilitic basilar meningitis, there is usually a decided cellular increase in the spinal fluid composed practically entirely of lymphocytes. In addition there is usually a positive Wassermann test and an abnormal colloidal gold curve. Even in the absence of a positive Wassermann reaction, however, there is usually enough in the spinal fluid findings, such as increase in cells and an abnormal gold curve, to confirm a suspicion of syphilis.

Still a third criterion for the diagnosis of choked disc due to syphilis is the response to treatment. In most cases antisyphilitic treatment is followed first by a rapid improvement in the subjective symptoms, notably the headache which is such a prominent feature of these cases. Ringing in the ears when present clears up quite rapidly and when there is a loss of hearing this too improves with treatment. The choked disc responds less rapidly. It may clear up entirely with treatment, or it may be quite resistive. In Case 2, despite the evidence for syphilis, operative interference was necessary in order to relieve the eye symptoms. With the removal of a chiasmal arachnoiditis the eye symptoms disappeared completely. In Case 4, despite the marked subjective improvement with antisyphilitic treatment, there was no recession of the choked disc at the time of discharge from the hospital. In the other cases, however, the choked disc disappeared completely (Cases 1 and 5) and almost completely (Case 3).

Too great emphasis cannot be placed on the necessity for careful observation of the visual acuity. It becomes too easy to attribute the choked disc to syphilis, and to lull oneself into a false sense of security in the belief that antisyphilitic treatment if continued long enough and intensively enough will result in complete disappearance of the choked disc. This is not necessarily true, for the choked disc may persist despite the most intensive treatment. It is essential during the course of treatment to test the visual acuity often—at least once each week. If there has been no response after a fair trial of treatment of 2 or 3 weeks, and the visual acuity is decreasing, steps must be taken to save the patient's eyesight. It may be necessary to perform a subtemporal decompression—but something must be done. If on the other hand, visual acuity does not decrease and the choking remains at the same level after a treatment period of 2 or 3 weeks, treatment may be continued provided the visual acuity is checked constantly. The response of the serology is of minor importance compared with the need for saving the eyesight.

Pathogenesis. Most of the clinical symptoms can be explained by a basilar meningitis, the cranial nerve palsies in particular. Other symptoms such as convulsions are not so readily explained on this basis. In a recent contribution Greenfield and Stern³ report 7 cases of syphilitic hydrocephalus in adults, 6 of them with choked disc. The clinical syndrome resembled that observed in our cases

with severe headache, convulsions, choked disc, and cranial nerve palsies. They assert that the underlying difficulty is a basilar syphilitic meningitis which produces either a communicating (1 case) or non-communicating type of hydrocephalus (4 cases). We have no pathologic studies of our cases but it is quite probable that the lesions in our cases was of a similar nature.

Recently Moore⁴ has reported a group of cases of acute syphilitic meningitis. Among 80 cases, one group of 26 corresponded closely to the type of case which we report. These cases were characterized by symptoms of "a rapidly developing hydrocephalus, *i. e.*, headache, nausea and vomiting, associated with symptoms of meningeal irritation. Neurologic examination in these cases showed only choked disc and stiffness of the neck." He looks upon this group as cases of acute syphilitic hydrocephalus associated with syphilitic infection of the meninges, in which there is disturbance of circulation of the cerebrospinal fluid by meningeal inflammation, mainly in the posterior fossa.

There is the further possibility that the choked disc is due to a local involvement of the optic nerve, the choking occurring from an interference with venous and lymph drainage from the retina as a result of the meningitis. This seems to have been the case in Case 2 of our series in which a choked disc of 2 diopters disappeared completely after the removal of thickened arachnoid over the optic chiasm and nerves.

The impression still prevails among clinicians that where there is evidence of choked disc in syphilis, there must be a gumma. The probabilities are much against gumma purely on the basis of statistics, for it is an established fact that gumma is a very uncommon brain lesion. Certainly the clinical features of our cases are not explainable by a solitary gumma, whereas they are readily explained by a syphilitic basilar meningitis. That this meningitis may assume gummatous characteristics has been demonstrated clearly by Jakob,⁵ but this is not equivalent to saying that the clinical picture is due to a solitary gumma. There is one more important characteristic of syphilitic meningitis, and that is that it is usually accompanied by an encephalitic process of syphilitic origin, so that it is in reality a meningoencephalitis. Some of the clinical signs are explainable only on this basis; and the failure of some of the symptoms to respond to treatment may have a similar basis.

There is probably much to be said for the conception of the syphilitic hydrocephalus of Greenfield and Stern. Four of our cases had a markedly increased intracranial pressure while in the fifth the pressure was at the high limit of normal. A choked disc which was due to a local meningitis process around the optic nerves and chiasm would not produce increased pressure in the head.

Management of Syphilitic Choked Disc. Having established the diagnosis of choked disc due to syphilis, the most important problem

is that of management. How are such cases to be treated? How long can one continue with antisyphilitic treatment? When must one consider other means of treatment?

Throughout the management of the case the prime consideration is the preservation of the patient's eyesight. The subjective complaints such as headache, dizziness, mental confusion and deafness will clear up rather quickly under treatment. The choked disc will usually persist so that the problem of saving the eyesight becomes the most important one with which the clinician must deal. It must be emphasized that no set formula for the duration of antisyphilitic treatment can be set down. The duration of treatment must depend on the condition of the vision. If on biweekly examination it is found that the visual acuity is unchanged, treatment may be continued with safety so long as this prevails, provided of course, it was not too low to begin with. If on the other hand, it is found that despite treatment, the visual acuity fails regardless of whether the choked disc is increasing or not, antisyphilitic treatment must be abandoned in favor of more effective means of preserving the eyesight, as for example, subtemporal decompression. It cannot be too strongly emphasized that the eyesight is the important consideration.

These principles are well exemplified in the treatment of our cases. In Case 1, the response to treatment of the choked disc and the visual acuity was rapid and gratifying, so that antisyphilitic treatment was carried out for a period of 2 weeks without trouble. In Case 2, however, the response of the patient to treatment was not rapid enough, the vision seemed to be getting worse, and a craniotomy was necessary to save the patient's eyesight. That this was done effectively is shown by the gratifying result some time after operation. In Case 3, the response was likewise slow, but here fever therapy was substituted for other methods with resulting rapid response in the recession of the choked disc. In Case 4, antisyphilitic treatment was carried out over 6 weeks with frequent testing of the visual acuity. The result was a complete recession of the choked disc and preservation of vision. In Case 5, despite active antisyphilitic treatment the choked disc continued to advance. It was felt that all the symptoms and signs were due to syphilis but preparation for surgical intervention was made in view of the advancing papilledema. Despite this, in the presence of normal visual acuity, more intensive treatment was given, with most gratifying results. The treatment formula varies therefore with each individual case. It cannot be otherwise.

One further point is essential. The diagnosis of choked disc due to syphilis should be made either by the neurologist or neurosurgeon, otherwise there will be too many cases of choked disc due to brain tumor which are treated for syphilis, particularly since it is well

known that brain tumor and a positive blood and spinal fluid serology may be present in the same case.

Conclusions. 1. Five cases of choked disc in central nervous system syphilis are recorded.

2. Four responded well to antisyphilitic treatment. The fifth was operated on with complete relief.

3. The underlying lesion is probably a basilar meningitis.

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THE DETECTION OF TUBERCLE BACILLI IN THE BLOOD STREAM BY THE LOEWENSTEIN TECHNIQUE AND AN ANALYSIS OF LOEWENSTEIN'S INVESTIGATIONS.

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EVER since 1930, Loewenstein^{*1} has reported numerous positive blood cultures of tubercle bacilli, not only in tuberculosis but also in diversified conditions of unknown etiology, such as rheumatic fever, chronic polyarthritis, dementia præcox and multiple sclerosis (Table 1). During this time, the results of other investigators who had employed his technique have been either negative or positive beyond a doubt in a few cases only (Table 2). Saenz,² of the Pasteur Institute in Paris, tried the Loewenstein method for 4 years, with no improvement in the results. He finally concluded that the old procedure of subcutaneous inoculation of whole blood into guinea pigs gave him better results than Loewenstein's method. Popper,³ of Maresch's Laboratory in Vienna, persisted in the use of the Loewenstein technique in 1600 cultures of blood from living persons, with only 8 (0.5%) undoubted positive results. Kolle and Kiister⁴ had only 7 (0.7%) positive cultures in a series of 953 cases. Each year many investigators have tried their hand at the work.

* Loewenstein's technique of culturing blood for tubercle bacilli consists of inoculating the sediment of citrated blood, freed of hemoglobin, on the surface of coagulated egg medium containing asparagin, glycerin and various salts. The inoculated culture tubes are completely sealed to prevent desiccation and incubated at 38° C. If no growth of tubercle bacilli is visible after 2 months' incubation, a smear of the surface of the medium is examined for microscopic evidence of tubercle bacilli (microscopic positive culture).

with similarly discouraging results, even after visiting Loewenstein's Laboratory.^{5,6,7, et al.}

TABLE 1.—RESULTS OF BLOOD CULTURES IN LOEWENSTEIN'S LABORATORY AS REPORTED BY LOEWENSTEIN, HIS COWORKERS AND OTHER INVESTIGATORS.

Type of case.	Total cases.	Positive cases.	Per cent positive.	Author of report.
Pulmonary tuberculosis	140	54	39	Loewenstein. ¹
With intestinal tuberculosis	?	?	100	Loewenstein. ¹
With fever	?	?	80	Loewenstein. ¹
Laryngeal tuberculosis	47	26	55	Wessely, Loewenstein. ⁶¹
Bone tuberculosis	67	26	39	Urgoiti. ⁶²
Urogenital tuberculosis	22	13	59	Lichtenstern. ⁶⁷
Skin diseases:				
Lupus erythematosus	33	19	58	Loewenstein (Kren). ⁶³
	48	3	6	Kissmeyer. ⁶⁶
Lupus vulgaris	31	11	35	Loewenstein (Kren).
	80	20	24	Kissmeyer.
	25	1	4	Konrad. ⁶⁷
Tuberculids	7	4	64	Loewenstein (Kren).
	17	1	6	Konrad.
Erythema induratum	40	21	52	Loewenstein (Kren).
Granuloma annulare	4	2	50	Konrad.
Erythema nodosum	14	12	86	Wallgren. ⁶⁴
	18	2	11	Kahlmeter. ⁶⁴
Polyarthritis:				
Acute	82	56	68	Reitter, Loewenstein. ⁶⁹
Chronic	80	27	34	Reitter, Loewenstein. ⁶⁹
Acute; chronic	1539	320	20	Loewenstein.
Diseases of the eye:				
Phlyctenular conjunctivitis, scleritis, iritis, uveitis, choroiditis	222	35	15	Loewenstein (Meller). ¹
Diseases of the central nervous system:				
Retrobulbar neuritis	6	4	66	Loewenstein.
Multiple sclerosis	111	47	42	Loewenstein.
Dementia præcox	359	142	39	Loewenstein.
	96	27	28	Kopeloff. ⁵
Chorea	9	5	55	Loewenstein.
Miscellaneous:				
Bronchial asthma	?	9	..	Loewenstein.
Sepsis; grippe	39	9	..	Popper. ⁶⁵
Sepsis (staph., strept.)	?	3	..	Mach, Mach. ⁶⁶

The difficulty of culturing tubercle bacilli from the blood has been encountered with the cultures of blood from living persons only. In such cases, the positive cultures were rare and the primary growths so scant that usually only 1 or 2 minute colonies appeared. With the blood obtained at postmortem of those who died of tuberculosis, there has been no such difficulty, for the cultures have frequently been positive and the growths usually abundant.^{8,9} Popper⁹ has reported as many as 80 to 90% positive blood cultures from those who died of tuberculosis.

TABLE 2.—RESULTS OF BLOOD CULTURES BY THE LOEWENSTEIN METHOD IN LABORATORIES OTHER THAN LOEWENSTEIN'S.*

Type of case.	Total cases.	Positive results.					
		Macroscopic.		Microscopic.		Macro. and micro. not specified.	
		No.	%	No.	%	No.	%
Tuberculosis (all types except of skin and eye)	5472	60	1.1	122	2.2	96	1.7
Skin diseases (tuberculous forms, including lupus erythematosus, erythema multiforme, erythema induratum, erythema nodosum)	633	3	0.4	12	1.9	9	1.4
Polyarthritides (acute; chronic; rheumatic fever)	467	1	0.2	15	3.2	7	1.5
Diseases of the eye (phlyctenular conjunctivitis, scleritis, uveitis, choroiditis)	160	1	0.6	5	3.1		
Diseases of the central nervous system (multiple sclerosis, dementia præcox, chorea minor)	455	1	0.2	8	1.7		
Total	7187	66	0.92	162	2.2	112	1.6

*The data in Table 2 was compiled from the reports of the following investigators: Abt; Arloing, Dufourt; Beck; Benedek; Bernhardt; Bonnet, Legros; Brugnoghe, Adant; Courmont; Corper, Damerow; Deist; Dimtza, Gutsche; Domingo; Dobszay; Ederle, Kriech; Emslie; Fetzer, Schmitz; Hager; Harnjanz, Kortman; Huttig; Iibuchi; Jontofsohn; Kadisch; Kolle, Küster; Laymon; Levin; Lotze; Koch, F.; Kalbfleisch, Kalbfleisch; Mach, Mach; Manteufel (Holtgrave, Kottman); Münster-Frank; Okell; Paraf, Abaza; Penfold, Butler; Petersen, Lederman; Popoff, Rousseff; Popper, H.; Popper, Bodart, Schindler; Richter; Rodiet, Nevot, Maillefer; Shapiro; Saegler; Saenz; Saenz, Pascal, Costil, Chapoulaud; Schramek; Schreiner; Sergent, Durand, Gaspar, Marcoux; Siegel, Singer; Stadler; Stempel, Bürki; Schwabacher; Szülc. These references are either indicated in the text or are listed alphabetically in the bibliography from No. 69 to No. 107, inclusive.

In our own country, there have been relatively few reports of the results of blood cultures by the Loewenstein method. These published results have almost all been negative.^{10,11,12,13} At Sea View Hospital, Loewenstein's method has been used since the end of 1930. Here, it was first used in 167 tuberculous cases, with 7 (4.2%) positive results.¹⁴ In 1933, the author with the aid of Dr. Singer¹⁵ continued the work, because Loewenstein's positive findings of the tubercle bacilli seemed to be in agreement with experimental, clinical and pathological experience. Experimentally, the ease with which disseminated tuberculosis occurs in susceptible animals, irrespective of the portal of entry, has been known for more than 50 years.^{16,17} Clinically, the occurrence in our tuberculous patients, especially infants, of tuberculous, phlyctenules, miliary tuberculosis of lungs, spleen and other organs, and of other evi-

dences of hematogenous dissemination of tubercle bacilli, was seen so often that it was felt that the invasion of bacilli into the blood stream must occur frequently. Pathologically, patients dying of tuberculosis invariably had tubercles and tubercle bacilli in one or more organs remote from the seat of the main lesion. Therefore, positive cultures were expected from those critically ill with tuberculosis.

TABLE 3.—RESULTS OF BLOOD CULTURES BY LOEWENSTEIN METHOD IN TUBERCULOUS PERSONS AT SEA VIEW HOSPITAL. (SIEGEL, SINGER.¹⁵)

Type of case.	No. of cases.	Specimens.	Results.		
			Negative.	Macroscopic positive.	Microscopic positive.
Adults—pulmonary, usually advanced or critical	332	759	708	2	49
Children—pulmonary, usually active and advanced	68	128	121	2	5
Umbilical blood of newborn of tuberculous mothers	13	13	11	1	1
Postmortem blood of newborn of tuberculous mothers	6	8	7	1	0
Postmortem blood of patients who died of tuberculosis	3	3	3	0	0
Total	422	911	850	6	55
Percentage of positive cases	1.4	13

The results of our first 5 months' work were disappointing. Of 150 cultures from 98 tuberculous persons, there were 3 (3%) macroscopic positive cultures and 10 (10%) microscopic positive cultures.* The macroscopic cultures grew on subculture and produced generalized tuberculosis on subcutaneous inoculation into guinea pigs. The microscopic positive cultures were negative to subculture and guinea-pig inoculation.

Since it was possible that we were not performing certain essential details in the method correctly, the author went to Loewenstein's Laboratory and worked under his supervision for 5 weeks. The work was then resumed at this hospital, with no changes in the procedure except for the use of water as a hemolytic agent instead of 3% acetic acid which had originally been employed. In spite of our previous experience and our work in Loewenstein's Laboratory, we were unable to improve our results. Of 663 specimens from 261 cases of all

* Macroscopic positive cultures were those in which colonies of tubercle bacilli were visible on the surface of the medium. If no growth was visible after 2 months' incubation at 38° C., a smear was made of the surface of the medium and examined under the microscope for acid-fast bacilli. If one or more clusters of acid-fast rods, resembling tubercle bacilli, were seen, the culture was called "microscopic positive." Smears which showed only a few isolated acid-fast rods were considered as negative and not included in the microscopic positive results.

forms of tuberculosis, usually advanced pulmonary tuberculosis, there were 1 (0.4%) macroscopic and 44 (16.9%) microscopic positive cultures. Only the macroscopic culture grew on subculture and produced tuberculosis after inoculation into guinea pigs. In part of this series, we investigated the effects of pneumothorax, thoracoplasty and surgery in bone tuberculosis in the production of a bacillemia. Before thoracoplasty, of 41 specimens from 29 patients, there was 1 microscopic positive culture. Of 200 blood specimens taken from these patients during and after operation, there were 16 microscopic positive cultures and 1 macroscopic culture. The macroscopic positive culture was obtained from a blood specimen taken immediately after the removal of the first 5 ribs in an adult with contralateral artificial pneumothorax. The postoperative course in all these cases was good, except in 1 case where the patient developed empyema. In pneumothorax, 21 specimens taken before the administration of air were negative, as compared with 2 microscopic positive cultures from 31 specimens obtained after 300 to 400 cc. of air had been given. In 7 cases of fusion operations for bone tuberculosis, all the preoperative and postoperative specimens were negative.

Thus far, of a total of 813 specimens from 359 tuberculous persons, we had 54 (15%) microscopic positive cultures and 4 (1.1%) macroscopic positive cultures. In spite of the few undoubted positive cultures (1.1%), we still felt that the tubercle bacilli were present in the blood stream of living tuberculous persons more frequently than we had demonstrated by the Loewenstein method. We, therefore, decided to compare Loewenstein's method with other methods.

With the aid of Mishulow,^{*18} we were able to compare the Loewenstein method (in which the hemoglobin is removed) with the whole blood method (in which the citrated blood is cultured without removal of hemoglobin). The latter method has successfully been employed by various investigators^{19,20,21,22} in detecting tubercle bacilli in the blood stream. Specimens of 4 to 14 cc. of blood were withdrawn from our tuberculous patients, and divided into two equal parts. One portion was mixed with sterile 0.4 cc. of 10% sodium citrate to prevent clotting, and was sent to Mishulow, who inoculated the whole blood directly, without preliminary removal of hemoglobin, on the surface of Loewenstein and of Bordet-Gengou media in 6 to 10 Petri plates. The other portion was cultured by us according to the Loewenstein method. The results of this series have already been published.¹⁸ Briefly, there were 98 specimens of blood from 63 tuberculous patients, most of whom were critically ill with tuberculosis or had clinical evidence of tuberculous bacillemia. Of the 98 specimens, there were 3 macroscopic positive

* Of the Research Laboratory, New York City Department of Health, under the Director, Dr. William H. Park.

cultures by the whole blood method, as compared with 1 microscopic and 2 macroscopic positive cultures by the Loewenstein method. In no instance were both portions of a divided specimen positive by both methods. In 2 infants with miliary tuberculosis, repeated blood cultures finally gave positive results by both methods. In a third case, only the whole blood method was positive; while in the fourth case, a culture by the Loewenstein method was microscopically positive. The results of this small series seem to indicate that it is unnecessary to remove the hemoglobin from the blood. Others^{2,20} also have shown that hemoglobin does not inhibit the growth of the tubercle bacilli.

Our search for the tubercle bacilli in the blood of tuberculous persons has not been abandoned. The use of saponin as the hemolytic agent²³ in the Loewenstein technique has been tried, with no increase in the number of our positive results. However, when large quantities of blood are available, saponin might still be of value, for it leaves a small sediment. At present, we are trying out Popper's modification of the Loewenstein technique with which Popper³ has had encouraging results.*

An old method, which we have not yet given an adequate trial, is the inoculation of blood into guinea pigs. This method is preferred by Saenz² after 4 years' experience with the Loewenstein technique. Saenz injects the whole blood sediment into the subcutaneous tissue of the thigh and observes the guinea pig for more than 8 months if necessary. Ninni²⁴ prefers the injection of the blood sediment into the lymph nodes.

A summary (Table 3) of our experience with the Loewenstein technique shows that, of 911 specimens from 422 tuberculous persons, there were 6 (1.4%) macroscopic positive cultures and 55 (13%) microscopic positive cultures. The 6 macroscopic cultures were undoubted cultures of tubercle bacilli that grew readily on subculture and produced disseminated tuberculosis in guinea pigs. Only 1 or 2 colonies were seen in the primary cultures of 5 to 10 cc. of blood. Therefore, the number of detectable tubercle bacilli in the blood stream are few, and repeated blood cultures are necessary. Frequently repeated blood cultures are also important, because one does not know when and how the degree of tuberculous bacilleemia varies. In pyogenic sepsis or malaria, there is a chill to tell the investigator when to take the blood specimen. In tuberculosis, there is no such guiding signal, and one depends on chance. When the clinical effects of a shower of bacilli into the blood stream, such as fresh tuberculids, are seen, it is often too late

* Popper allows the blood specimen to remain at 38° C. in a fluid nutrient medium of asparagin, di-sodium phosphate, mono-potassium phosphate, magnesium phosphate, sodium citrate, glycerin and saponin. At the end of 10 to 14 days this is centrifuged and the sediment is inoculated on the surface of Loewenstein medium. The cultures are sealed and kept in the incubator at 38° C. for 2 months.

for a culture, for most of the bacilli disappear quickly from the blood stream.^{6,19}

The 55 (13%) microscopic positive results did not grow on sub-culture nor did they produce evidence of tuberculosis in guinea pigs. The significance of the microscopic positive cultures has not yet been determined. Until more is known about them, we shall regard them as doubtful positive results. It is obvious that the total percentage of positive results can be markedly increased by combining the microscopic and macroscopic positive results under the one heading, *positive cultures*, such as Loewenstein has done.

Our 6 macroscopic positive cultures were from various types of cases. In 1 instance, 2 minute colonies were grown from the blood of the umbilical cord. In this case, the placenta had a tuberculous area, 2 cm. in diameter. The mother died of tuberculosis 18 hours after the delivery. The newborn was a 7-month premature who died within 3 hours, with no clinical evidence of tuberculosis. The necropsy findings in the newborn were negative except for atelectatic areas in the lungs. A culture of its heart blood gave an abundant growth of tubercle bacilli in all of the culture tubes.

There were 4 other macroscopic positive cultures in our series. Two were from adults with advanced pulmonary tuberculosis. In 1 of these cases the blood specimen was taken immediately after a first-stage thoracoplasty operation in which the first 5 ribs were removed. The postoperative course was uneventful. The patient also received pneumothorax on the contralateral side. In the other case the patient was critically ill with pulmonary and intestinal tuberculosis. In 2 instances, the macroscopic positive cultures were from infants, 9 and 10 months respectively, with pulmonary and generalized miliary tuberculosis. Additional blood specimens from these 2 infants were also positive by the whole blood method, as already mentioned.

In 12 other instances, smooth, glistening, chromogenic colonies of acid-fast bacilli grew which proved to be non-pathogenic. These bacilli grew on nutrient agar at 38° C. in a few days and on Loewenstein medium at room temperature. They were saprophytic contaminants which almost all investigators who have used the Loewenstein technique have encountered. They have also been found in Loewenstein's Laboratory.²⁵ According to Loewenstein, they "cannot be differentiated by their shape and staining characteristics from true tubercle bacilli." They indicate the importance of sub-culture and virulence tests, especially of colonies obtained in non-tuberculous conditions.

Discussion. The problem of tuberculous bacillemia is an old one, and its history is important in the evaluation of Loewenstein's results. Even before Koch's discovery of the tubercle bacillus, Villemin,¹⁶ in 1868, had shown that the causative agent of tuberculosis was in the blood stream, by producing tuberculous lesions in

a rabbit subcutaneously inoculated with blood from a tuberculous person. After the discovery of the tubercle bacillus, one of the first problems to stimulate research was the detection of the bacilli in the blood. The first to report successful results was Weichselbaum,²⁶ in 1884, with his report of tubercle bacilli in the smears of the postmortem blood clots of 3 cases with acute miliary tuberculosis. To these, Meisels²⁷ added 8 more positive results postmortem, in cases of acute miliary tuberculosis. In chronic miliary tuberculosis, the smears of blood clots were negative.

In 1891, Liebman²⁸ aroused unusual interest in tuberculous bacillemia by reporting the presence of tubercle bacilli in smears of drops of blood of 39 out of 44 tuberculous patients after tuberculin injections. Controls from 20 normal persons were negative. However, his results were not verified by others.^{29,30} Some 20 years later, several investigators reported the presence of acid-fast bacilli in the blood stream of almost all living tuberculous persons.

Rosenberger³⁸ (1909), using the sediment of 2 to 10 cc. of whole citrated blood, was able to report 125 positive cases from patients with tuberculosis. With the Stäubli-Schnitter⁴⁹ method Kurashige,³¹ in 1911, reported 100% positive smears in 155 tuberculous cases, and about 60% positive results in 34 apparently normal persons. Suzuki and Takaki³² followed, in 1912, with 500 positive cases out of 517 with tuberculosis. In the same year Liebermeister³³ reported many positive blood smears from tuberculous and non-tuberculous persons. His positive results in 26 out of 28 cases of pulmonary tuberculosis, 70 scrofulous patients, 37 persons with rheumatic fever, and several with erythema nodosum and angina remind one of Loewenstein's results 20 years later.

However, not all workers had such consistently good fortune. Some investigators were not successful in finding tubercle bacilli in any of their cases, even in those with tuberculosis.^{29,34} Such a marked discrepancy in the results of a procedure apparently so simple as the microscopic examination of a blood smear naturally created doubt as to the reliability of the method. It was soon seen that there were many sources of error. A scratch on the slide, shreds of fibrin and debris, hemin crystals, crystals of fuchsin and incompletely decolorized smears were only a few of the things which might simulate the appearance of the tubercle bacillus. It was also soon discovered that not all acid-fast bacilli are tubercle bacilli. Rabinowitsch³⁵ reported that more than 60 different acid-fast forms were found between 1882 and 1902. These were present in almost all living forms, in plants, mammals, birds, reptiles and fish. They were also found in air and water, and even in distilled water.^{36,37} Brem's experience with distilled water is instructive. Following Rosenberger's³⁸ technique, he found acid-fast bacilli in the blood smears of such non-tuberculous conditions as malaria, typhoid and pneumonia. Searching for the explanation he eventually

found non-pathogenic acid-fast bacilli in his distilled water and in all solutions made from it.

The use of animal inoculation to verify the results of blood smears varied with the different investigators. Of 125 cases positive by smear, Rosenberger³⁸ reported the results of intraperitoneal guinea-pig inoculation of blood sediment in 2 instances only. Both of these were said to be positive. Liebermeister,³³ in 1908, trying guinea-pig inoculation of whole blood from 50 tuberculous persons, found death from "inoculation tuberculosis" in 40% of the cases. No description of the lesions in the positive guinea pigs was given. Since these results were lower than the 100% he had obtained by blood smear, he concluded that the inoculation of guinea pigs was not sensitive enough. Suzuki and Takaki³² claimed that animal inoculation proved their smear findings, which were positive in 510 cases. Like Liebermeister,³³ they had no controls nor did they describe the lesions in the positive inoculated animals. Where investigators described the findings in their guinea pigs, it was apparent that their diagnosis of inoculation tuberculosis was often doubtful. In most such instances^{39,40,41} the workers depended on Ziehl-Neelsen smears of the blood and tissue of the guinea pig when there were no macroscopic or even microscopic tuberculous lesions 6 to 8 weeks after inoculation. Kennerknecht⁴¹ also relied on temperature changes in her inoculated animals after subcutaneous injection of 0.5 cc. of O.T. This tuberculin test was done about 14 days after intraperitoneal inoculation of 2 cc. of the blood sample. With such criteria of inoculation tuberculosis and no controls, one does not wonder that the blood of many or of all the tuberculous and non-tuberculous cases were said to be positive. Where the animal inoculation was well controlled and the lesions in the inoculated animals were undoubtedly tuberculous, there were no positive results in non-tuberculous persons, and few positive results in tuberculous persons. Kahn,⁴² in 1913, was able to collect from the literature only 32 (6.2%) out of 512 tuberculous cases in which the results of guinea-pig inoculation could be accepted as positive.

Blood cultures for tubercle bacilli were also tried. Until 1929 the positive results were less than by guinea-pig inoculation. Of 558 tuberculous cases reported from various sources, from 1906³⁵ to 1929, Wilson⁴³ was able to collect only 6 instances (1%) in which tubercle bacilli were undoubtedly cultured from the blood of living persons. Blood cultures for tubercle bacilli were rarely positive until 1930, when Loewenstein began to report his many positive results.

Loewenstein's results are striking for the types of conditions in which he reports the tubercle bacilli in the blood stream and for the high percentage of positive results in tuberculous and non-tuberculous cases. These unusual results naturally create doubt among the many investigators who have failed to verify them (Table 2),

especially as the Loewenstein method is not difficult. In his own laboratory his technician has been able to do almost all of his cultures alone. Furthermore, his medium and method, although excellent, have not been so unusual as to warrant such striking results.

The coagulated egg, asparagin, glycerin, starch or potato sugar (Kartoffelzucker) and various salts that make up the Loewenstein medium have been used for many years in making media for the tubercle bacillus. Its glycerin was introduced by Nocard and Roux⁴⁴ in 1887. Its asparagin, as a source of nitrogen, was used in 1894 by Proskauer and Beck,⁴⁵ who also recommended the various salts later used by Loewenstein. The coagulated egg was introduced by Dorset⁴⁶ in 1902, and the glycerinated egg, by Lubenau⁴⁷ in 1907. In 1930, about 25 years later, Loewenstein¹ reported the use of all these ingredients in his Congo-red medium.

Although his medium is good, Loewenstein has not depended on it alone. In 1926, Petragnani⁴⁸ introduced his malachite-green medium of potatoes, peptone, glycerin, 4 whole eggs and 1 yolk to 150 cc. of milk. This malachite-green medium, containing asparagin instead of peptone, has been constantly used by Loewenstein with his Congo-red medium. The tubercle bacilli seem to grow well on both media. The disadvantage of the Loewenstein Congo-red medium is that it contaminates easily and liquefies, thus spoiling the culture. This occurs so readily that Loewenstein never does a blood culture without using 1 to 2 tubes of the modified Petragnani malachite-green medium. On this modified Petragnani medium, Loewenstein has had about 55% of his total macroscopic positive cultures, while about 45% have been on his Congo-red medium.

The technique of culturing tubercle bacilli was introduced more than 50 years ago (1883) by R. Koch, who first grew the tubercle bacilli from various tuberculous tissues on coagulated serum. As early as 1905, Loewenstein⁴⁸ himself reported the culture of tubercle bacilli from the heart blood of experimentally infected guinea pigs. In 1906, Rabinowitsch³⁵ cultured the tubercle bacilli from the blood of a patient with pulmonary tuberculosis. In 1909, Anderson⁵⁰ spread the centrifuged sediment of citrated blood on glycerin potato medium, sealed the tubes with paraffin, and observed them for 2 months before discarding them as negative.

The removal of hemoglobin from the blood goes back to 1908, when Stäubli⁵¹ used 3% acetic acid to hemolyze the blood, centrifuged the mixture, decanted the supernatant fluid and studied the sediment. In 1930, Loewenstein¹ advised the same procedure, because he felt that hemoglobin inhibits the growth of the tubercle bacilli. In 1932, he stressed the use of distilled water instead of acetic acid. Distilled water as a hemolytic agent had been employed by Burville-Holmes³⁷ in 1910. In 1912, Duchinoff⁴⁰ stressed

complete removal of hemoglobin by repeated washing with distilled water, a procedure which Loewenstein strongly advocates.

In addition to the complete removal of hemoglobin, Loewenstein stresses the use of 15% by volume of sulphuric acid if contamination is suspected. The principle of using a chemical substance to kill contaminants without destroying the tubercle bacilli was successfully employed by Uhlenhuth,⁵² in 1908, with antiformin. In 1909, Schnitter⁴⁹ used antiformin on the sediment of blood hemolyzed by acetic acid, according to the Stäubli method. This procedure, the Stäubli-Schnitter method, became popular in the search for tubercle bacilli in the blood. Substitutes for antiformin, such as sodium hydroxid and hydrochloric acid soon appeared. In 1924, Loewenstein advised the use of 15% by volume of sulphuric acid in culturing contaminated material, such as sputum, urine and feces. In 1930, he introduced its use in culturing blood.

Since 1930, in spite of the many positive results, Loewenstein has frequently tried to improve his method and medium. As a hemolytic agent he used acetic acid (3% to 10%) for approximately his first 4500 blood cultures, but this gave an objectionable pasty sediment. To overcome this he tried saponin (from 0.5% to 2%) instead of acetic acid. In 1011 cultures, he reported 156 positive results, but discarded the saponin as "macroscopically visible colonies did not develop on the cultures." In December, 1931, he began to use distilled water which he still employs. During the years of 1930 and 1931, he not only varied his hemolytic agents, but also tried the effects of potassium hydroxid, varying from 0.5% to 2%, and 0.5 to 1 cc. of 15% by volume of sulphuric acid.

In his media, he has frequently tried new ingredients and different proportions of the old ingredients. Petraghani's⁴⁸ medium was almost always used with asparagin instead of peptone, and with varying amount of eggs and glycerin. Potato sugar replaced potato flour. For several months serum was added and occasionally asparagus water. Loewenstein's Congo-red medium also underwent many changes. The number of eggs and the amount of glycerin were usually equal to the egg and glycerin content of the modified Petraghani medium. At times the amount of asparagin was increased. For several months tomato juice, occasionally milk and even gum arabic were added. For a while water extracts of asparagus, beans and fish were also added.

Loewenstein's investigations may be criticized from two points of view—his definition of a positive blood culture and his conception of a control. For him a culture is positive either if colonies appear which he considers typical of tubercle bacilli (macroscopic positive), or if a smear of the surface of the medium, which has no visible growth after 2 months' incubation at 38° C., shows acid-fast forms which he considers tubercle bacilli (microscopic positive).

Most of the macroscopic positive cultures shown to the author

by Loewenstein had growths of typical colonies of tubercle bacilli. The primary blood cultures grew unusually well and luxuriously, unlike the minute colony or two which appeared in the primary growths obtained by other workers. In fact, his primary macroscopic cultures usually resembled the abundant growth of subcultures. Occasionally, he called yellowish or whitish growths positive which appeared rather atypical, like contaminants, either acid-fast saprophytes or non-acid-fast organisms. However, Loewenstein seemed to have no doubt that these were typical cultures of tubercle bacilli from blood sediment. He, therefore, regarded subculture and guinea-pig inoculation as unnecessary.

Although Loewenstein has had extensive experience with the tubercle bacillus, it would still be preferable if he confirmed his macroscopic positive cultures with virulence tests, especially his cultures from the blood of non-tuberculous persons. Almost all workers who have cultured blood for tubercle bacilli have had acid-fast colonies which have proved to be saprophytic on subculture and virulence tests. Of 10 macroscopic cultures from 300 tuberculous cases, Popper had 6 saprophytic strains which he believed were contaminants. Saenz reported that 3 out of his 9 macroscopic cultures in 500 tuberculous cases were non-pathogenic "paratubercle bacilli." In 120 tuberculous cases, Corper and Damerow¹⁰ had 2 macroscopic cultures only, both of which proved to be saprophytic bacteria. Even in Loewenstein's Laboratory, Fanjul and Gerzner²⁵ reported 8 macroscopic cultures of saprophytic "pseudotubercle bacilli" in 45 cases with positive blood cultures.

There were relatively few microscopic positive cultures during the author's 5 weeks' visit to Loewenstein's Laboratory. In all instances, the acid-fast forms resembled tubercle bacilli. In 1 smear, a few scattered forms were seen in one field only. The remainder of this smear and smears from 2 other culture tubes of the same blood specimen were negative. In 1 other case, several groups of acid-fast bacilli were present. Smears from two other culture tubes of the specimen were filled with non-acid-fast contaminants.

The significance of a "microscopic positive culture" is doubtful. Almost every worker has seen acid-fast material in smears of the surface of media with no macroscopic growth. Some have had microscopic positive results only; others have had an occasional macroscopic positive culture (Table 2). Almost all the subcultures and guinea-pig inoculations of the microscopic positive cultures have been negative in the hands of workers other than Loewenstein, even though distinct acid-fast rods, singly or in groups like typical tubercle bacilli from colony growths, were seen. It is conceivable that in some instances the tubercle bacilli were dead and, therefore, could not grow; that at other times only slight growth occurred, so that it could not be seen with the naked eye. It is possible that the growth of the tubercle bacilli might stop with a minute colony

hidden away along the side or bottom of the culture tube. However, it is also well known that acid-fast material might be artefacts or bacilli that are not tubercle bacilli. Loewenstein, himself, stated, in 1932, that saprophytic "acid-fast bacteria cannot be differentiated by their shape and staining characteristics from true tubercle bacilli." He even considered as erroneous the many positive results of the smears of blood sediments which Rosenberger, Liebermeister, and Kurashige had formerly used to demonstrate the presence of tubercle bacilli in the blood.

Unfortunately, Loewenstein does not separate in his publications the total number of his microscopic from his macroscopic positive cultures. In his reports, he refers to them as "positive blood cultures." In his records, he also referred to them as "positive," until February, 1932, for about his first 7000 cultures. Thereafter, he indicated which of his positive cultures were "macroscopic" or "microscopic." It was soon seen that the former comprised about 55% to 60% of his total positive results.

The total number of Loewenstein's microscopic and macroscopic positive cultures has varied considerably from time to time. At times, most of his positive cultures had distinct colonies on the surface of the medium (macroscopic positive). Such was the case when the author visited Loewenstein in May, 1933. At other times, all or almost all of his cultures had no macroscopic colonies, and his positive results were based upon microscopic examination of a smear of the surface of the medium (microscopic positive). During certain periods there were many microscopic and macroscopic positive cultures. During other periods, however, almost all of his cultures were negative, even after microscopic examination. The cause of these marked variations in results has been attributed by Loewenstein chiefly to uncontrollable variations in his media and his centrifuge. At one period he claimed that the use of saponin as a hemolytic agent was the cause of his microscopic positive results. In view of these variations in Loewenstein's unusual results, it is important to know the nature of his controls and his results in these controls.

Loewenstein claims that he has had over 7000 negative control specimens to substantiate his work; that his cultures of undiagnosed blood samples, from such controls as healthy persons and those with non-tuberculous conditions, as gonorrhea, syphilis and cancer, have been negative. The details of this statement can be learned from the reports of the following workers who have sent him undiagnosed blood specimens.

Siegl,⁵³ of the "Wiener Kinderklinik," used blood samples from children with active tuberculosis, inactive tuberculosis, and negative reaction to tuberculin. Each sample of blood was divided into three parts. One part was sent to Loewenstein, another to Maresch, and the third part was inoculated into guinea pigs. In the entire series of 177 specimens, there was only 1 which was positive in

the inoculated guinea pigs. This positive blood was from a child with active tuberculosis. In Maresch's laboratory there were 3 microscopic positive cultures all from the children with active tuberculosis. Loewenstein, however, reported 28 positive blood cultures. He reported positive cultures in 13.5% of the specimens from the children with active tuberculosis, 18.9% from those with inactive tuberculosis, and 23.9% from those with negative tuberculin and no clinical evidence of tuberculosis. Wallgren,⁵⁴ like Siegl, also reported that Loewenstein had positive blood cultures in 3 children with repeatedly negative intracutaneous tuberculin tests to 10 mg. O.T. One child had erythema nodosum and 2 had rheumatic fever, with no clinical evidence of tuberculosis.

In skin conditions, Loewenstein seems to have had many positive blood cultures in specimens sent undiagnosed from clinically non-tuberculous persons.^{55,56,57} In Delbanco's⁵⁵ series of 15 specimens from patients with tuberculous skin conditions, there was 1 (7.2%) positive culture; in 42 specimens from patients with gonorrhea, there were 7 (16.6%) positive cultures; and in 23 specimens from those with other non-tuberculous skin conditions, there were 7 (30.4%) positive cultures. Loewenstein has had positive blood cultures in such skin conditions as neurodermatitis, eczema, acne vulgaris, folliculitis,⁵⁵ furunculosis, erythema pernio, impetigo, acne vulgaris;⁵⁶ lymphatic leukemia, mycosis fungoides, acne vulgaris.⁵⁷

Kopeloff's experience with Loewenstein is also noteworthy. Samples of blood were first sent from 42 psychotic patients clinically free of tuberculosis, and from 12 normal doctors and nurses. Kopeloff⁵⁸ divided each specimen of blood into 4 parts, gave each part a different identification number, sent 3 to Loewenstein and cultured 1 himself according to the Loewenstein technique. In this series of 54 persons, Loewenstein reported 20 positive blood cultures, 13 macroscopic and 7 microscopic, all from the psychotic patients (dementia præcox, psychoneurosis, manic depressive and involutional melancholia). None of the specimens from the normal persons was positive. All the cultures by Kopeloff were negative. Kopeloff⁵ continued with the experiment. As Loewenstein received more blood specimens, he began to report macroscopic positive cultures in the clinically normal persons as well as in the psychotic patients. To complete the experiment, Kopeloff also sent 50 specimens of blood from 25 patients with active tuberculosis. In none of these specimens from cases of active tuberculosis did Loewenstein obtain a positive blood culture. In the entire series, Loewenstein had 31 macroscopic positive cultures distributed as follows:

	No of cases.	Macroscopic positive.
Active tuberculosis	25	0
Dementia præcox	96	21
Other psychoses and neuroses	19	5
Normal persons	54	5
(Healthy doctors and nurses)		

The macroscopic positive results were cultures of virulent tubercle bacilli as shown by subcultures and virulence tests.⁵

In spite of these many unexpected positive results,^{5,53,55, et al.} Loewenstein claims that 7000 negative "control" specimens substantiate his work. What he evidently means by a control is a case with a negative blood culture. Once he reports the blood positive, he claims that he has demonstrated the presence of the tubercle bacilli in the blood—no matter what the clinician thinks about the case. Under experimental conditions, in which only cases with negative blood culture are considered as controls, one should use other types of controls to prove that the positive cultures come from the blood only and not from other sources.

Loewenstein has reported many other unusual findings that make adequate controls essential. He found tubercle bacilli not only in the blood of those with dementia præcox but also in their spinal fluid. He has also reported positive cultures in the blood and spinal fluid of several children with chorea. Reitter and Loewenstein⁵⁹ have reported positive cultures from the umbilical blood of 3 newborn, whose mothers had rheumatic fever with repeatedly positive blood cultures during their pre-partum period. In these instances, the newborns were normal, with negative tuberculin to 100 mg., and no clinical evidence of tuberculosis after observation periods of 5 to 12 months. The numerous positive results in non-tuberculous skin conditions have already been mentioned.^{55,56,57, et al.} In addition, he has had positive results in such diversified conditions as polycythemia rubra, Hodgkin's disease, bronchial asthma and sepsis.

Several workers have tried to control his work by giving Loewenstein part of the blood specimen and sending the rest to other laboratories or culturing it themselves. While Loewenstein reported many positive cultures from tuberculous, non-tuberculous and clinically healthy persons, the results in other laboratories were negative.^{5,53} Mathiesen⁶⁰ had a similar experience. He sent blood specimens of 51 cases of tuberculous skin diseases to Maresch's Laboratory and to Loewenstein. In Maresch's Laboratory there were no macroscopic growths and only 7 microscopic positive cultures, negative to subculture. Loewenstein reported 13 positive blood cultures. Konrad⁵⁷ also sent half of each blood specimen from persons with skin diseases to Maresch and to Loewenstein. Again, of 134 cases, Loewenstein reported 30 positive cultures, as compared with only 4 microscopic positive results in Maresch's Laboratory.

Loewenstein's explanation for the differences between his results and those of others, has been that the work in his own laboratory is superior. He cannot, however, expect this explanation to be accepted until his many positive results, especially the microscopic positive cultures, are verified by subcultures and virulence tests, and until he has satisfactory controls.

Summary. 1. Of 911 blood specimens from 422 tuberculous persons at this hospital, there were 6 (1.4%) macroscopic positive cultures and 55 (13%) microcopic positive cultures by the Loewenstein technique. The macroscopic positive cultures were undoubted cultures of tubercle bacilli according to subculture and virulence tests. The microscopic positive cultures were not definitely proved to be cultures of tubercle bacilli, since subcultures and animal inoculation gave negative results.

2. The disparity between Loewenstein's results and those of other investigators still exists after 5 years of research.

3. Loewenstein's investigations may be criticized from two points of view: his definition of a positive blood culture and his conception of a control.

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(Titles have been omitted for sake of brevity.)

BRONCHOGENIC CARCINOMA.

AN ANALYSIS OF 54 CASES WITH A ROENTGENOLOGICAL CLASSIFICATION.

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THE marked increase in the number of cases of bronchogenic carcinoma in recent years, observed in the Department of Radiology at our Institution, stimulated this review of our material. Long regarded as a rarity,¹ primary malignancy of the lung is today recognized as a tumor which occurs relatively frequently. Whether this increased incidence represents a real or apparent increase in the actual number of cases is still a mooted question.² In a series of 2209 autopsies, at the University of Vienna Pathological Institute,³ Rogers found an incidence of 2.3% of bronchial carcinoma. We have observed it in 1.2% of 1773 necropsies. Prior to 1926, only an occasional case appeared in our records. In 1933, however, 23 were recognized, and during the first 9 months of the past year 19 additional cases have appeared.

In view of the recent advances in the surgical^{3,4,5} and roentgenologic treatment^{6,7,8} of the disease, early diagnosis has become increasingly important, for those lesions which are still localized are more amenable to treatment; whereas advanced cases, in the main, are hopeless. With this in mind, we have reviewed the cases of bronchogenic carcinoma in our hospital since 1926 (Chart I).

In all we have made a diagnosis in 123 instances. Fifty-four cases which were regarded as proven beyond doubt have been selected for detailed study. Of these, 26 were proven by bronchos-

copy with biopsy, 20 by necropsy, 4 by biopsy of accessible metastatic foci, and 4 were initially diagnosed by the presence of malignant cells in the pleural fluid sediment.

CHART I.—INCIDENCE OF BRONCHOGENIC CARCINOMA.

Year.	Total number hospital cases.	Number of cases of primary carcinoma of lung.
1926	9,429	4
1927	9,911	4
1928	10,028	14
1929	12,150	12
1930	13,263	14
1931	13,915	17
1932	14,261	16
1933	14,976	23
1934	11,204*	19
Total	109,177	123

* To October 1, 1934.

The Roentgen ray in most cases gave the original clue, but was not regarded as positive proof,⁹ even though the roentgenograms may have been classical. Cases in which the bronchoscopist reported bronchial stenosis with intact bronchial mucosa alone were also discarded as unproven.¹⁰

Age and Sex Incidence. (Chart II.) The data reveal 72% of cases in males; 63% of the cases occurred between the fourth and seventh decade. Our youngest patient, a boy aged 12, has been under our observation for 3 years; our oldest patient was a man, aged 73. Except for the extreme youth of our youngest case, our findings are in accordance with those of other observers.

Location of the Primary Growth. (Chart III.) The location of the neoplasm in the bronchial tree is deserving of comment. Rogers,³ Funk,¹¹ and Atkin¹² state that each side is about equally involved, but our figures show that the right side is slightly more susceptible to tumor growth. In our series, 29 occurred on the right side, 22 on the left and 3 in the trachea. These figures bear out Fried's² assertion, that bronchogenic carcinoma is more frequently observed on the right side. Manges also confirms this finding.¹³

The main bronchi were the most common sites of the primary tumor, with the upper primary divisions next in frequency. This is a fortunate circumstance, since it is obviously much more difficult to visualize tumors bronchoscopically when located in the more remote minor bronchi. Our findings are not in agreement with Rogers,³ who found the superior bronchi more frequently involved than the main bronchi. Manges⁷ and Fried's² data are more in accordance with our own.

Duration of Symptoms Before Hospitalization. (Chart IV.) The symptoms before hospitalization ranged from an acute onset to a duration of 3 years or more. About 20% presented symptoms of

less than 3 months' duration before admission to the hospital, while approximately half of our cases gave a time incidence of from 3 to 12 months.

CHART II.—AGE, SEX, INCIDENCE

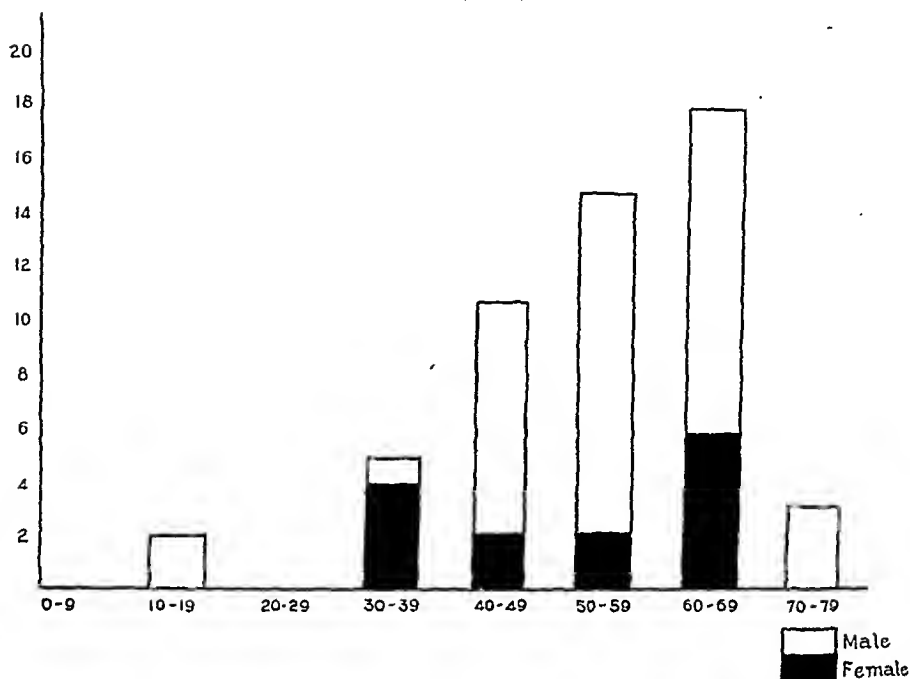


CHART III.—LOCATION OF PRIMARY GROWTH.

Right.				Left.	
Main bronchus	13			12	Main bronchus
Upper bronchus	8	Trachea	2	5	Upper bronchus
Middle bronchus	2	Carina	1		
Lower bronchus	2			1	Lower bronchus
Not stated	4			4	Not stated
Total	29			22	

Total, 54.

CHART IV.—DURATION OF SYMPTOMS BEFORE HOSPITALIZATION.

Time.	Number of cases.
0 to 3 mos.	11
3 to 6 mos.	13
6 mos. to 1 yr.	11
1 to 2 yrs.	3
2 to 3 yrs.	4
3 yrs. or more	3
Undetermined	9

The usual mode of onset was that of an insidious, afebrile pulmonary picture. In 16 cases (30%), the onset was atypical; of these, 5 were admitted to the hospital with a diagnosis of pneumonia

and 1 as acute cardiac decompensation. Five complained of symptoms referable to osseous metastases, 2 to symptoms of cerebral involvement, 1 to dysphagia caused by mediastinal metastases, 1 because of jaundice caused by occlusion of the common bile duct by a metastatic deposit adjacent to the head of the pancreas, and 1 presented a massive thrombosis of the venous circulation of the neck, chest, shoulders and arms.

SYMPTOMS. A study of the symptoms, according to age groups, is presented in Chart V.

CHART V.—SYMPTOMS.

Age groups.	Cough.	Hemoptysis.	Chest pain.	Weakness and loss of weight.	Dyspnea.	Hoarseness.
0 to 9 . .	0	0	0	0	0	0
10 to 19 . .	2	0	1	1	0	0
20 to 29 . .	0	0	0	0	0	0
30 to 39 . .	4	2	3	2	2	4
40 to 49 . .	11	8	9	8	6	2
50 to 59 . .	16	9	14	13	8	1
60 to 69 . .	15	9	12	11	9	3
70 to 79 . .	2	0	1	2	0	0
Totals . .	50	28	40	37	25	10

Cough, usually attributed to a bronchitis, occurred in 92% of the cases, and was the most frequent, as well as the earliest symptom. The severity of the cough varied from a slight, unproductive, irritating hack to severe harrassing paroxysms with purulent, blood-streaked expectoration. The severity of the cough was not indicative of the extent of the lesion, but in the main was dependent upon the degree of endobronchial obstruction and irritation. However, cases were noted in which the cough was minimal in the presence of a completely stenosing lesion. These, in the main, presented a diffuse luminal encroachment of the bronchus by peribronchial invasion.

Exceedingly profuse foul-smelling sputum was not encountered in this series. In no instance did we find that the usually accepted clinical picture of lung abscess overshadowed that of the bronchogenic neoplasm, although distal pulmonary suppuration was frequently found at bronchoscopy and necropsy.

Blood-streaked sputum and the occasional loss of a small amount of blood was present in 52% of our series. Frank hemorrhage was uncommon.

Chest pain was encountered in 74% of the cases. At the onset, it was mild in nature, but progressed, in some instances to the agonizing intense and persistent pain of extensive pleural involvement. We look with great suspicion upon those afebrile subjects who present chest pain, when associated with a hacking, unproductive cough.

Loss of weight and weakness were observed in 72% of the patients. Neither was appreciably present before the sixth month of the

disease. They are, as a rule, manifestations of well-advanced cases. The relative rarity of cachexia was so striking that it is deserving of special comment.

Dyspnea was also a relatively late symptom, and is probably due to extensive pulmonary involvement, mediastinal metastases or fluid. It occurred in 46% of our series. Hoarseness was present in but 18%, and may be ascribed to involvement of the recurrent laryngeal nerves by secondary deposits.

Four cases were incorrectly diagnosed; 2 were attributed to tuberculosis, and proved to be bronchogenic carcinoma at autopsy. In the third instance, the initial diagnosis of upper lobe tuberculosis was only eventually disproved after 4 bronchoscopies had been performed and a successful biopsy was obtained from the right upper bronchus. This tumor was unusually radiosensitive, and the improvement with radiotherapy was so remarkable over a period of 2 years that the diagnosis was questioned up to the time of the conclusive biopsy. The fourth case was diagnosed as a carcinoma of the thyroid with multiple metastases. At necropsy, a silent primary bronchogenic neoplasm was found.

In some instances, metastases overshadowed in significance the pulmonary symptoms, and were the first indication of the presence of malignancy. Rogers³ states that as many as 44% of a series of 50 cases had initial symptoms caused by metastases. We have found this to be true in 18% of our cases. In 1 of these, the primary bronchial lesion was almost imperceptible, but the patient presented a well-advanced picture of intracranial metastatic malignancy. We have found no relationship between the size of the primary focus and its propensity to metastasize.

CHART VI.—METASTASES.

Autopsies, 20.

Glandular	11
Bone	9
Liver	8
Lung	8
Adrenal	6
Kidney	6
Pleura	5
Pancreas	4
Spleen	3
Skin	2
Brain	2
Thyroid	2
Heart	3
Venous thrombosis	2
Gall bladder	1
Stomach	1

In our series of 20 cases with necropsy findings, metastases (Chart VI) to the hilar, mediastinal and cervical lymph nodes were most frequently encountered with bone, lung and pleura, liver, adrenal, kidney and brain, following in the order mentioned. The mesenteric glands were also occasionally involved. Skin metastases were present in 2 of our necropsied cases (10%), and 5 of our total

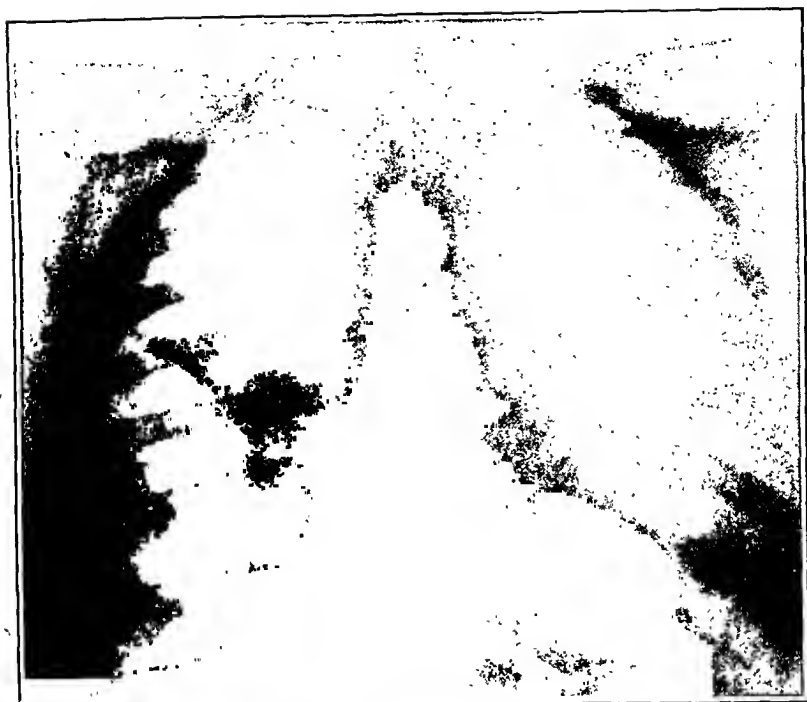


FIG. 1.—Group 1. Early. Hilar involvement, with secondary parenchymal infiltration. No elevation of the diaphragm; no fluid nor retraction of mediastinum.

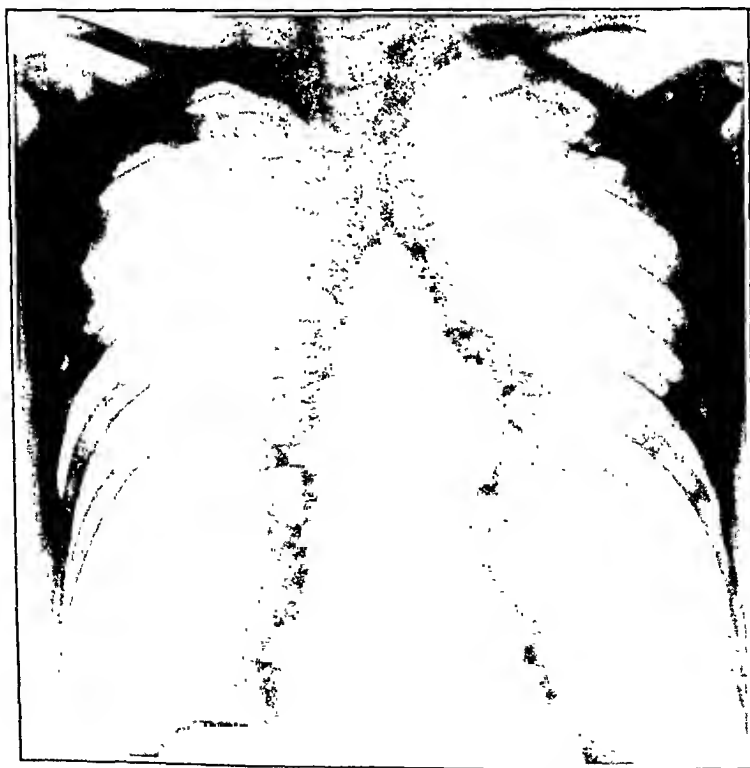


FIG. 2.—Group 1. Early. A sharply circumscribed, dense hilar opacity, with no parenchymal involvement; no diaphragmatic nor mediastinal displacement.



FIG. 3.—Group II. Moderately advanced. Carcinoma of right lower bronchus, with hilar and parenchymal involvement. Partial lower lobe collapse.



FIG. 3a.—Group II. Moderately advanced. Same as Fig. 3 following diagnostic pneumothorax.

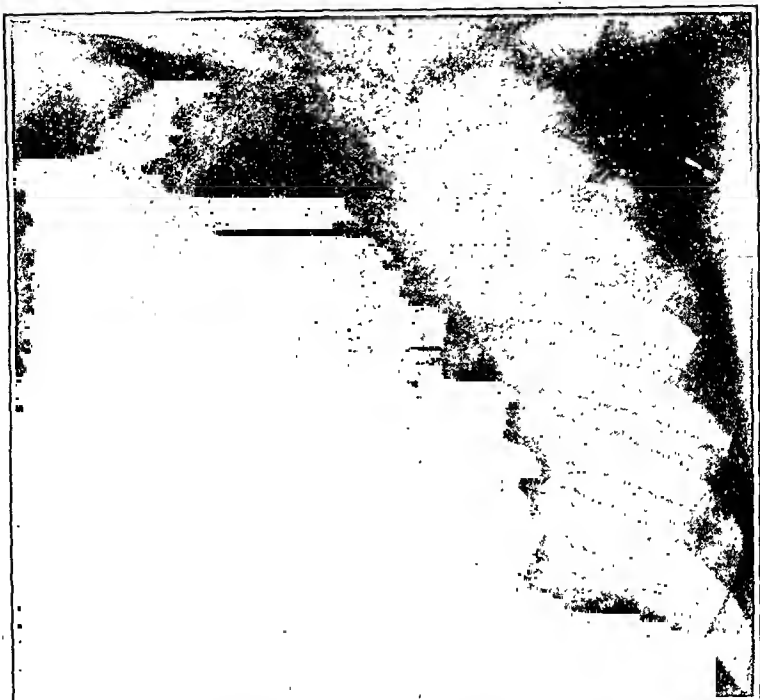


FIG. 4.—Group II. Moderately advanced. Atelectasis resulting from a bronchogenic carcinoma of the right main bronchus in a child 12 years of age.

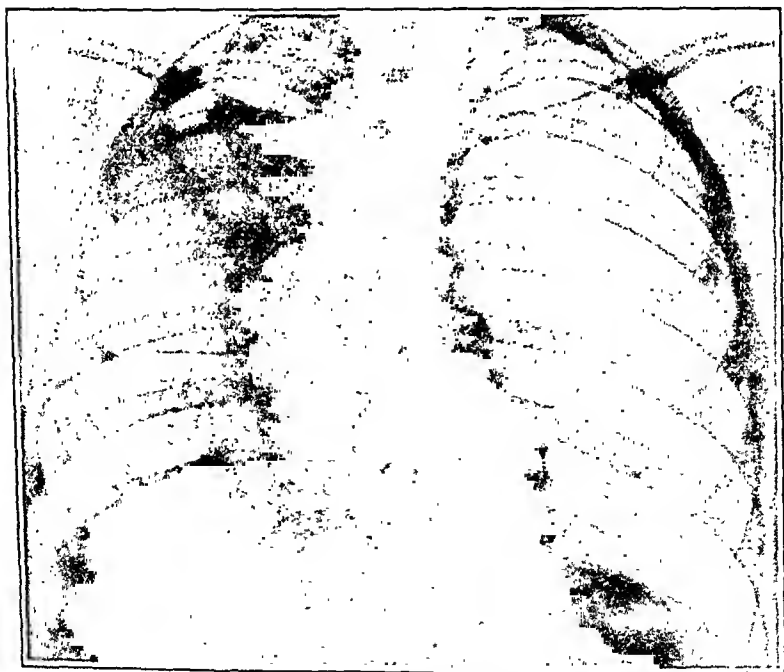


FIG. 4a.—Group II. Moderately advanced. Same as Fig. 4. Result 7 weeks later, after 10,800 milligram hours of radium.



FIG. 5.—Group III. Advanced. Formerly considered alveolar type. Note marked elevation of diaphragm and diminution in size of lung field.

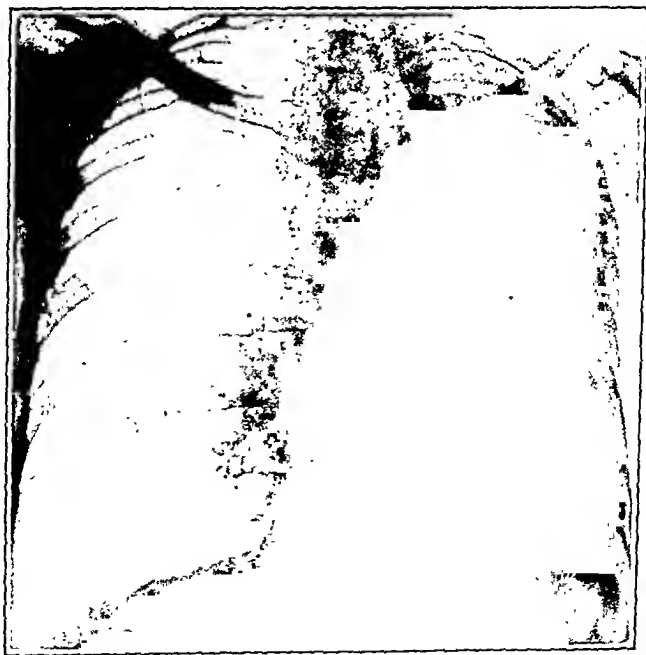


FIG. 6.—Group III. Advanced. Deviation of trachea toward affected side, loss of diaphragmatic shadow in overlying effusion, shift of mediastinum toward affected side, compensatory emphysema of right lung.

series. They appeared as small, hard, nodular deposits, confined mainly to the thorax and upper extremities, with normal overlying skin. The relative frequency is worthy of comment.

Once the symptoms become well established, the course, in most instances, is progressively down grade and most discouraging. Thirty-seven of our cases have died, 29 within 1 year after the diagnosis was established, 7 within 3 years and 1 after 10 years. The latter proved to be an angioendothelioma of the right main bronchus. It is questionable whether this case should be considered in the malignant group.

The radiotherapeutic results have been very discouraging, since in most of those treated, the disease was so far advanced, relief was all that could be hoped for. We were occasionally encouraged by the subsidence of cough and improvement in the radiographic picture; this was looked upon as due to diminution in the size of the neoplasm, with resultant improved drainage. We recognize, however, that an atelectatic area may at times aërate spontaneously. Two cases yielded more satisfactory results. One, a man, aged 60, was in comfort for 2 years, and the second, a boy, aged 12, is still attending school, the diagnosis having been established 3 years ago.

Our results of the treatment of osseous metastases have been more gratifying. In several instances, ossification of the rarefied neoplastic areas occurred, with complete subjective relief.

Surgery also leaves much to be desired. Those cases which present evidence of neoplastic hilar involvement are obviously too far advanced for satisfactory results. Since 72% of our series presented evidence of root infiltration, and in many of the other cases this finding was obscured by overlying fluid, one readily sees how restricted the field for surgery becomes. Those cases are best fitted for radical intervention in which the lesion is confined to a minor bronchus or the parenchyma, and which appear on the roentgenogram as an isolated, well-defined infiltrated area within the lung substance, preferably near the periphery.

Analysis of Roentgenologic Pulmonary Findings. (Chart VII.) A roentgenographic examination was made in 51 cases; in 44 of these the films were available for study. They were grouped according to the degree of pulmonary involvement from the following criteria:

CHART VII.—ANALYSIS OF ROENTGEN-RAY FINDINGS.

	Early.	Moderately advanced.	Advanced.	Total.
Number of cases	14	11	19*	44
Neoplastic hilar involvement	12	10	10	32
Hilar plus secondary bronchial infiltration	9	11	11	31
Diminution of size of affected lung field	9	11	15	35
Elevation of diaphragm	1	11	10	22
Retraction of mediastinum	0	1	10	11
Fluid	0	1	12	13
Bilateral hilar infiltration	2	8	9	19

* Findings obscured in 7 cases because of effusion.

1. Neoplastic hilar involvement—the presence of a definitely visible, unilateral circumscribed hilar shadow.

2. Hilar involvement plus invasion of the bronchial tree, extending radially into the parenchyma. This is looked upon as indicative of (a) venous engorgement, (b) bronchial infection, (c) peribronchial neoplastic invasion, (d) or the earlier degrees of bronchial stenosis. In most instances the findings are due to a combination of these factors in varying degrees.

3. Diminution in size of the affected lung field, the result of partial or complete atelectasis from bronchial obstruction.

4. Elevation of the diaphragm on the affected side, due to pulmonary atelectasis or secondary to inclusion of the phrenic nerve by mediastinal metastatic involvement.

5. Retraction of the mediastinum toward the affected side.

6. The presence or absence of fluid.

7. Bilateral hilar infiltration—in the presence of a definite unilateral lesion, increase in the size of the contralateral hilar shadow is indicative of secondary infection or metastatic involvement.

8. Bronchography by means of iodized oil.

9. Artificial pneumothorax. Bronchography and artificial pneumothorax are special radiographic procedures¹⁴ occasionally employed and are strictly hospital measures. The former may be performed by the bronchoscopist at the time of bronchoscopic examination (active method); we, however, have obtained more satisfactory results by anesthetizing the faucial pillars and pharynx followed by direct instillation of the iodized oil under the fluoroscope (passive method). This procedure permits better visualization of that particular portion of the lung field under suspicion. Its chief value lies in the demonstration of a complete bronchial stenosis; in early cases without blockage it is of little value. Of the 13 cases so studied in our series, bronchial obstruction was demonstrated in 6 instances (46%).

The chief value of artificial pneumothorax lies in the demonstration of deposits in the parenchyma or on the pleura, and may occasionally be of help in diagnosing a lesion in a smaller bronchus. We have 1 such case in our series.

With large pleural effusions more decisive roentgenograms may occasionally be obtained immediately after thoracentesis. The microscopic examination of the sediment of the aspirated fluid is of great value. Malignant cells were demonstrated in 7 of 17 specimens examined. In 4 of these instances it was the first evidence of conclusive proof of the existence of pulmonary malignancy; in the remaining 3 it was confirmatory evidence after the diagnosis had been established by other means.

We find, from a study of these criteria, that bronchogenic carcinoma can be divided into early, moderately advanced and advanced cases. This classification is essentially an anatomico-pathologic one,

based upon the bronchial growth and its resultant pathology. It is not to be considered strictly clinical, although in the main the clinical course runs quite parallel. Fried,² whose classification we would follow mainly, found it difficult to classify these tumors from a gross pathologic viewpoint, but came to the conclusion that the tumors could be divided into an early and a far-advanced group.

Based upon the radiographic studies, we suggest the following classification:

1. **EARLY.** Hilar opacity with little or no fuzzy parenchymal infiltration. Size of lung field normal or slightly diminished. Absence of pleural fluid. Rarely, a localized small parenchymal deposit independent of the hilar shadow.

2. **MODERATELY ADVANCED.** As above, with the addition of definite inequality of the lung fields, elevation of the diaphragm, slight or moderate parenchymal involvement, occasionally mediastinal retraction, pleuritis and, more rarely, a small amount of pleural exudate.

3. **ADVANCED.** Hilar and pronounced parenchymal infiltration. Retraction of the mediastinum toward the affected side. Lung shrinkage, elevation of the diaphragm. Fluid frequently obscuring the entire radiographic picture.

GROUP I. Early. Fourteen (32%) of the 44 cases available for study fall into this group. Slight diminution in the size of the involved lung field was present in 9 of the cases in this group. No retraction of the mediastinum was observed. The only constant finding was the presence of a hilar opacity, with moderate secondary peribronchial infiltration (Figs. 1 and 2).

GROUP II. Moderately Advanced. There are 11 cases (25%) in this group. They showed a definite diminution in the size of the affected lung and elevation of the diaphragm. Retraction of the mediastinum was present in but 1 instance; fluid also was noted but once (Figs. 3, 3a, 4 and 4a).

GROUP III. Advanced. Nineteen (43%) of our series are in this group. Fluid was a frequent finding, in many instances completely obscuring the radiographic picture. Retraction of the mediastinum, with elevation of the diaphragm, was noted in about half of the cases. The presence of both these signs is usually indicative of a stenosing bronchial lesion, with concomitant atelectasis. Hilar opacities with marked peribronchial involvement, often sufficiently dense to obliterate lung markings, are frequently seen when not obscured by the overlying pleural fluid (Figs. 5 and 6).

Films were available for study in 17 of the 20 necropsied cases. Comparing the extent of the lesion as diagnosed by Roentgen ray with the gross pathologic findings, we find agreement in 12 cases. Two cases diagnosed as moderately advanced by Roentgen ray were found to be rather extensive; 1 case diagnosed as advanced was found to have been caused by a polyp; and 2 cases were missed

completely by Roentgen ray, 1 of which was found to have a small retrocardiac lesion in the left minor lower bronchus, and the other presented a minimal lesion in a main bronchus, the presence of which had been unsuspected.

Conclusions. Fifty-four proven cases of primary bronchogenic carcinoma are reported, with an analysis of the symptoms. We have suggested, from a radiographic standpoint, a classification into three groups—early, moderately advanced and advanced; criteria for each division have been presented.

Of 51 cases studied roentgenographically, in 23 instances a positive diagnosis was made; in 12, the diagnosis was suggested. Pleural effusion obscured the findings in 4. The diagnosis was not made in the remaining 12 cases.

Of the above cases, 31 were bronchoscoped; in 26 of these the diagnosis was conclusively established. Three cases in which the diagnosis was not made were unusual in that the lesion occurred in a subdivision of the main bronchus and was, therefore, inaccessible to the bronchoscope; in 2, no biopsy was taken.

Our statistics show that bronchoscopy is the most valuable and positive single diagnostic aid. However, since roentgenograms are readily obtained and entail no discomfort to the patient, a Roentgen ray study should be the initial diagnostic procedure. Though the film may be negative, bronchoscopy should be urged in all cases in which there is a suspicious clinical picture. It is precisely these very early lesions, not demonstrable by Roentgen ray, that may be most benefited by treatment.

The outlook for a patient with bronchogenic carcinoma is, indeed, discouraging. Until recently, the prognosis was invariably fatal. Within the past few years, more encouraging reports have appeared in the literature. It is impossible to state whether the future method of treatment will be surgical^{4,6,17} or radiotherapeutic,^{7,13} or a combination of both.¹¹ The important problem is to diagnose the case sufficiently early in order to allow surgical intervention or efficient radiotherapy. The disease is now passing into that stage of its history where the diagnosis is no longer sealed with a forlorn hope, but rather by its early detection opens the possibility of radical or palliative therapy. It is with this in mind that we reviewed our material and proposed the aforementioned classification.

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ESTIMATION OF BASAL METABOLIC RATE FROM PULSE RATE AND PULSE PRESSURE.

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ALTHOUGH the determination of the basal metabolic rate is now within the reach of most internists following the recent improvements in the technique and cost of the necessary apparatus, there remain a considerable number of physicians who do not find it convenient for financial or technical reasons to install such apparatus in their offices. Read¹ has attempted to calculate the basal metabolic rate from determinations of the pulse and pulse pressure. It can be appreciated that a formula for accurately predicting the basal metabolic rate in a large percentage of cases, with minimal error, would prove useful to the general practitioner.

Investigators had previously discussed the relationship between basal metabolism and pulse rate²⁻⁴ and the increase in pulse pressure accompanying an elevated metabolic rate.^{5,6} Rough estimations of the B.M.R. from the pulse rate and blood pressure had been attempted frequently. Assuming that the pulse and blood pressure changes may in many instances reflect quantitative variations in the amount of work done by the circulatory system in transporting oxygen, Read attempted to correlate these findings with the B.M.R. Three hundred determinations of the B.M.R. were made using the

Sanborn Benedict portable calorimeter; in all instances estimations of the blood pressure and pulse rate were also made. From these, Read computed coefficients of correlation between the various factors, and derived a multiple prediction formula for the estimation of the B.M.R. as follows:

$$\text{B.M.R.} = 0.683 (\text{P.R.} + 0.9 \text{ P.P.}) - 71.5$$

where P.R. is the pulse rate and P.P. the pulse pressure. He found that in 300 cases, when pulse rate and pulse pressure were estimated under the same basal conditions as were required for the determination of the B.M.R. that the latter could be calculated with an error not more than 10% in 60% of the cases; 91% of the cases showed an error not more than 20%. He concluded from his observations that most individuals respond to variations in metabolic rate with proportionate changes in pulse rate and in pulse pressure; a few showed disproportionate changes in the one with little or no change in the other; and that a combination of the two gives a better measure of the circulatory system's response to variations in metabolic rate than either alone. In all of these calculations, he excluded patients with a systolic pressure over 160 (except young patients with marked toxic goiter) because this was attributed in most instances to pathologic changes in the cardiovascular-renal system and not to a physiologic response of the circulatory system to increased metabolism; also omitted were patients with auricular fibrillation or other cardiac arrhythmias.

Several years later, the formula was modified (on the basis of a greater number of estimations) to the following:⁷

$$\text{B.M.R.} = 0.75 (\text{P.R.} + 0.74 \text{ P.P.}) - 72$$

At a later date, Gale and Gale,⁸ studying over 1000 cases, developed a simpler prediction formula:

$$\text{B.M.R.} = \text{P.R.} + \text{P.P.} - 111.$$

which, in their hands, gave more accurate results than the Read formula.

Certain investigators have found results similar to those of Read⁹⁻¹⁶ while calculations by others were quite at variance.¹⁷⁻²¹ Rosenberg¹³ commented on the observation that when the B.M.R. rose above 45 per cent, the calculated value (Read) tended to fall below the B.M.R. Kemeny¹⁴ called attention to the parallelism of actual and estimated B.M.R. chiefly in cases approaching the normal. Bertheau¹¹ stressed the accuracy of the formula in cases of hypothyroidism; Cameron *et al.*¹⁷ found the formula to be inaccurate in children, which has been attributed to the increased and labile pulse rate in childhood.

More recently Read and Barnett²² have reinvestigated this problem, taking into consideration the surface area, age and sex of the

individuals. It has been shown that heat production and cardiac minute volume parallel each other rather closely. Minute volume can be roughly estimated clinically from the pulse rate and pulse pressure. It was found that the products of the pulse pressure and pulse rate were higher and the heat production lower in women than in men. Separate formulæ were then derived for the two sexes. By means of correlation tables, the following formulæ were determined.

$$\text{Men: Cals./sq. meter/hr.} = \frac{\text{P.R.} \times \text{P.P.}}{200} + 27$$

$$\text{Women: Cals./sq. meter/hr.} = \frac{3 \times \text{P.R.} \times \text{P.P.}}{700} + 24$$

From these the basal metabolic rate is then calculated in the usual manner as the percentage above or below the fixed normal standards for a given age and sex. In 100 consecutive cases (21 males and 79 females), Read and Barnett found the following:

Error not more than:

5%	10%	15%	20%	25%
59	78	94	98	100

It must be remembered that the above error signifies the difference between the observed and the calculated rates expressed in per cent deviation from normal—*i. e.*, if the observed B.M.R. were +20 and the calculated +25, the error is considered a 5%.

A series of 100 ambulatory patients (88 females and 12 males) was studied in this hospital. From these were excluded all patients with arrhythmias, hypertension, or other cardiovascular disturbances which produce alterations in the pulse rate and pulse pressure obviously not caused by changes in blood flow. Basal metabolic rates were determined in the usual way by the Sanborn Benedict apparatus, and at the same time, determinations were made of the blood pressure and average pulse rate; all determinations were made under basal conditions. From these data, the B.M.R. was calculated by three methods (Read-Barnett, Read formula 1924, and Gale and Gale). The results may be summarized as follow:

Deviation from the observed B.M.R. not more than:

	5%	10%	15%	20%	25%	Correlation coefficient observed: predicted.
<i>Read-Barnett Formula</i>						
1. U. of P. data	41	67	87	93	98	0.845
2. Read-Barnett data	59	78	94	98	100	
<i>Read Formula (1924)</i>						
1. U. of P. data	38	67	86	92	96	0.807
<i>Gale and Gale Formula</i>						
1. U. of P. data	35	54	75	84	92	0.820
2. Gale and Gale data	27			74		

Using standard statistical methods, it is found that there is no significant difference between the results obtained by the three

methods in our series of 100 patients. The correlation coefficient between pulse rate alone and B.M.R. was 0.623.

Discussion. The estimation of B.M.R. from pulse-rate and pulse-pressure data is crude, for once in 10 or 20 cases an individual prediction will be 20% too high or too low. This renders the method of little use clinically. In our series of 100 cases the various equations are not significantly different in the correlation they give with the

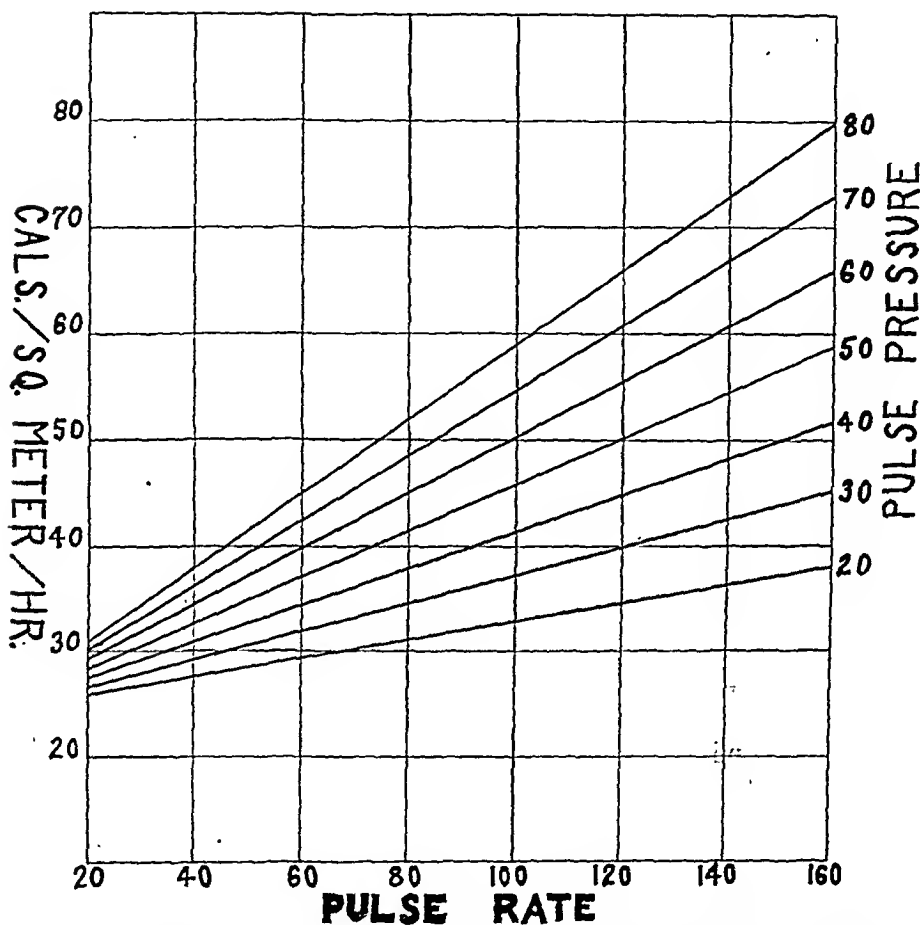


FIG. 1.—Nomogram for estimation of basal metabolic rate in females by means of Read-Barnett formula.

observed basal metabolism. The importance of disturbing factors not included in the formula is so great that attempts to refine the formula or to select the best are rather futile. If one desires to use the Read-Barnett formulæ, they can be used most conveniently in the form of a nomogram, as shown in Figure 1. The results are read directly in cal./sq. meter hr., which result is then compared with the standard accepted reading for individuals of that age and

sex, and the B.M.R. calculated as the percentage of the reading above or below the accepted standard. Gale and Gale's rule, easily remembered and requiring only mental arithmetic, gives results not significantly less good.

Conclusion. 1. The B.M.R. cannot be predicted from pulse rate and pulse pressure with significant accuracy and consistency to render the method a substitute for measurement by indirect calorimetry.

2. Gale and Gale's rule can be conveniently memorized and used, and in our hands gave results not significantly less accurate in 100 cases than the more elaborate calculations of Read and Barnett.

3. If calorimetric estimation of the B.M.R. is not possible because of technical or financial difficulties, calculation of the B.M.R. from pulse pressure and pulse rate data is more accurate than attempting to guess this figure from either observation taken separately.

4. If one wishes to employ the formulæ of Read and Barnett, the use of nomograms is recommended.

We are indebted to Dr. J. Harold Austin for assistance in our statistical analysis and preparation of the nomogram.

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ANGINA PECTORIS AND HEART BLOCK,

AS SYMPTOMS OF CALCAREOUS AORTIC STENOSIS.

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IN recent years much attention has been directed to aortic stenosis caused by calcific lesions of the semilunar valves. That the lesion is not rare is shown by various statistical studies. Thus McGinn and White¹ found aortic stenosis in 1.8% of 6800 autopsied cases of all types of disease. Yet the diagnosis was made in only $\frac{1}{3}$ of the cases. This is a common experience. The classical physical signs are often lacking, and no distinctive symptomatology has been described.

I wish here to stress the frequency of the syndrome of angina pectoris and of conduction disturbances in patients with aortic stenosis. Not a few isolated reports of this association appear in the literature, but it has not been adequately emphasized. Years ago Allbutt² remarked that angina pectoris is not uncommon in patients with aortic stenosis. Mackenzie³ believed that stenocardia in patients with aortic stenosis was due to associated changes in the heart muscle. Cabot⁴ writes, "In its clinical picture aortic stenosis is peculiar not only in its proneness to occur in elderly men, but also in the frequency of precordial pain, of faintness on exertion, and of angina pectoris." McGinn and White note that 19% of their patients with aortic stenosis had angina pectoris. Margolis⁵ reports 42 patients with aortic stenosis of whom 4 had angina pectoris. Tuohy and Eckman⁶ point out that anginal seizures can occur in such patients whose coronary arteries are normal.

I have records of 19 private patients with aortic stenosis. Of these 4 had classical angina pectoris. The greater frequency of the anginal syndrome in a clinical rather than a pathologic series of

cases is understandable, because in many instances aortic stenosis gives rise to no symptoms and the patient dies of some intercurrent disease.

Case Abstracts. CASE 1.—A. K., a woman, aged 63, was first seen when she was 53, at which time she had no symptoms referable to her heart. She had no rheumatic history, but had had frequent sore throats. The heart was not enlarged. There was a rough systolic murmur at the aortic area, which was transmitted upward to the neck. The heart sounds were of good quality. The pulse was regular and full. The blood pressure was 90/75.

Three years later she noted for a time occasional substernal oppression on exertion. The same symptom recurred for a short period 2 years later. At 60 this symptom became more disabling and constant. Climbing stairs or walking uphill provoked a pressure sensation under the sternum which radiated to the shoulders and up the neck and compelled her to stop until the pain was relieved. Examination at this time revealed a heart considerably enlarged to the left, with a heaving apex beat in the anterior axillary line. There was a systolic thrill in the second and third interspaces, to the right of the sternum. Here a rough systolic murmur, and a musical diastolic murmur were audible. The latter was transmitted down the sternum. There was a systolic murmur at the apex.

The anginal symptoms persisted. Three years later increasing shortness of breath and a sense of oppression in the chest developed rather quickly, and the patient became bedridden. Examination revealed marked dyspnea and orthopnea, with bilateral massive hydrothorax, but no ascites nor edema. The heart findings were unchanged. On about the tenth day of this acute illness, shortly after being transported to a hospital, she suddenly experienced agonizing pain over the precordium, which radiated down the left arm, her face turned an ashen gray and there was leaden cyanosis of the lips. She was very restless, and vomited several times. She became unconscious and died within 40 minutes. It was thought that she had had an acute coronary occlusion.

The electrocardiogram taken 3 years before death showed negative *T* waves in all leads. A year later, marked left axis deviation was noted. In addition, occasional records showed marked variation in the character of the *Q-R-S* complexes. They had a supraventricular origin, but were aberrant in form, often changing from beat to beat. At one time the electrocardiogram showed transient bundle-branch block.

Autopsy (Dr. S. Jacobson, 4½ hours after death). The heart weighed 430 gm. There was marked hypertrophy of the left ventricle. All of the valves except those at the aortic orifice were normal. The cusps of the aortic valves were extremely calcified and thickened, with irregular calcified vegetations. The opening between the aortic valves was very small and rigid, measuring barely 2 mm. in diameter. The arteriosclerotic process did not involve the mouths of the coronary arteries. The coronary arteries themselves were straight and soft, with minimal sclerosis. There was no thrombus in these arteries, and there was no cardiac infarction. There was only very slight atheroma of the aorta. There were no gross scars in the myocardium, but there was some microscopic increase in the interstitial connective tissue.

CASE 2.—A man, aged 44, had had frequent attacks of tonsillitis as a boy. He had had no arthritis. At 24 he was rejected by an insurance company because of a heart lesion; 5 years later he began to be slightly short-winded, and to experience occasional sticking apical precordial pain on lifting objects. Two years prior to his first visit he commenced to experience a pinching sensation near the apex of the heart on exertion and on

excitement. Six months later attacks appeared in which the left hand would become icy cold, and this would be followed by a pressing pain along the inner aspect of the forearm. Of late this symptom had become worse. Particularly in the morning when he left the house after breakfast the left forearm became cold and he experienced a sense of pressure to the left of the sternum which compelled him to stop. He experienced similar pain on intercourse.

Examination showed a well-built man with slight cyanosis of the lips. The lungs were clear. The liver was not enlarged. Fluoroscopy revealed a huge left ventricle, the apex extending to the axilla. The other chambers were normal. The apex beat was forceful. At the aortic area there was a systolic thrill and a rough systolic murmur. A diastolic murmur was heard at the aortic area and transmitted to the apex. At the apex there was a loud systolic murmur which was transmitted to the axilla. The blood pressure was 110/65; the pulse was rather small. The electrocardiogram showed left axis deviation and sharply negative deep *T* waves in Leads I and II.

He has been under observation for 2 years following his initial examination, and the symptom of left parasternal pain on excitement or on exertion which compels him to stop his activities has persisted.

CASE 3.—M. I., a man, aged 48, had had gonorrheal arthritis 25 years previously. There was no rheumatic history. He had frequent sore throats until tonsillectomy was performed 5 years prior to his first examination. He had obtained insurance at the age of 28, but 8 years later had been rated up for a murmur. Four years prior to his examination he began to experience attacks of substernal oppression which radiated to the neck and down both arms, associated with a choking sensation and difficulty in breathing. These attacks occurred on walking. They appeared more readily in cold or windy weather. The attacks gradually became more frequent and more severe, so that at the time of examination he could walk only a block before being compelled to stop. During the 8 previous months he had had a number of spontaneous attacks of similar pain at rest.

He was a well-built man of good color. The lungs were clear. The liver was not enlarged. Fluoroscopy revealed considerable enlargement of the left ventricle and of the left auricle, and slight general dilatation of the aorta. The first heart sound was of good quality. There was a musical systolic murmur at the apex. There was a faint systolic thrill and a rough systolic murmur at the aortic area. Here there was also heard a diastolic murmur which was transmitted to the apex. The blood pressure was 130/90; the pulse was small. The radial arteries were not sclerotic. The electrocardiogram showed only left-axis deviation.

CASE 4.—E. K., a man, aged 37, had had several attacks of rheumatic arthritis as a young man and a heart lesion discovered at about the age of 20. He had had few symptoms referable to the heart, but recently had tired easily and had noticed some shortness of breath on walking rapidly, and had had several attacks of faintness.

He was a well-built man. The lungs were clear, the liver not enlarged. Fluoroscopy revealed moderate enlargement of the left ventricle and some dilatation of the ascending aorta. There was a systolic thrill at the aortic area, as well as a rough systolic murmur. A diastolic murmur was also heard here and transmitted along the left sternal margin. At the apex there was a systolic murmur transmitted to the axilla. The blood pressure was 120/70.

For about 1½ years following the first examination there was little change in his condition. He experienced frequent joint pains in the ankles, wrists and fingers, and occasional shooting precordial pain, worse on exertion.

He never had fever. His heart rate always ranged around 90. At this time he took 16 cc. of tincture of digitalis in 3 days, and on the fourth day felt very faint and experienced soreness in the precordium, which radiated down the left arm. Examination revealed complete heart block, with a ventricular rate of 50, an auricular rate of 100, and many extrasystoles. Four days later normal rhythm was restored.

Following this he was quite inactive and felt well for 3 months, when one night he awakened with precordial pain which radiated down the left arm and which lasted all the following day. He felt very weak. For a few days previously he had experienced fleeting pains in the joints and a slight sore throat. Examination revealed no change in the physical findings. There was normal sinus rhythm, with a heart rate of 90 to 100. No fever followed this upset, but he felt weak and the precordial pain occasionally recurred. One week later the rate suddenly dropped to 60, and the day following to 48, and the electrocardiogram again revealed complete heart block. At this time he complained of pain in the left arm. Ever since then there have been frequent spontaneous changes in the cardiac mechanism, from sinus rhythm to partial heart block to complete heart block. At rest there was the usual sinus rhythm, with a heart rate of 80, but walking caused a drop in rate to 60 with the appearance of heart block and occasional pain in the left arm. The sedimentation rate of the red blood cells at this time was 3 hours.

About 1 month after the first appearance of the heart block he began to experience precordial oppression radiating down the left arm, on walking about a block. This symptom persisted ever after, and indeed gradually became more severe. The appearance of heart block on exertion too was common.

Three years after he was first examined, and 13 months after the first appearance of heart block, he developed a fulminating lobar pneumonia involving both lower lobes. On the third day he suddenly complained of intense epigastric pain. His color became ashen, the pulse feeble, and he died after about 1 hour. No autopsy was obtained.

CASE 5.—D. C., a man, aged 34, who had never had rheumatic fever or sore throats, had been told at 24 years of age that he had a valvular lesion. He had had no symptoms referable to the heart until 6 weeks previously, when he noted substernal pressure, dyspnea and orthopnea which prevented him from falling asleep. These symptoms had persisted.

Examination revealed a rather pale man, not dyspneic at rest. The lungs were clear. The liver extended 3 finger breadths below the costal margin. Fluoroscopy revealed huge enlargement of all of the chambers of the heart, particularly of the left ventricle, with some fullness of the pulmonary conus. The aorta was small. The first heart sound was of good quality, and at the apex there was a loud systolic murmur which was transmitted to the axilla. At the aortic area there was a systolic thrill, and a rough systolic murmur was audible. A diastolic murmur was heard along the left sternal border. The heart rate was 36, with frequent extrasystoles. The electrocardiogram revealed complete heart block, with ventricular extrasystoles. The blood pressure was 170/80.

The patient did well on diuretics, particularly of the mercurial type, but heart failure recurred and he finally died of that condition 1½ years after his first visit. Complete heart block had persisted during this whole period.

No autopsy obtainable.

CASE 6.—M. H. (No. 374837), a woman, aged 52, had had no rheumatic episodes. For 20 years she had had intermittent swelling of the ankles. Diabetes was discovered 2½ years previously. For the past year and a half she had experienced gradually increasing dyspnea on exertion, and occa-

sional attacks of nocturnal dyspnea. Two months previously she began to have an unproductive cough, which persisted. Five days before admission to the hospital she was awakened from sleep by an attack of severe dyspnea and orthopnea, with sharp precordial pain which radiated to the back, was aggravated by cough and relieved by lying down. The pain and dyspnea lasted an entire day. She was then up and about. On the night before admission to the hospital she was again seized with intense dyspnea and precordial pain.

Physical Examination on Admission. She was profoundly dyspneic and cyanotic, perspiring profusely, with frequent cough, and looked acutely ill. There were moist râles throughout both lower lobes. The heart was slightly enlarged. The first sound was feeble, the pulmonic second sound accentuated, and there was gallop rhythm at the apex. The pulse was very weak and rapid. The blood pressure was 160/100. The liver was felt 4 finger breadths below the costal margin. The white blood cell count was normal. She did not rally. Her condition grew progressively worse; she became comatose and died on the fourth day after admission.

On the day following admission the blood pressure dropped to 94/78. The temperature ranged from 101 to 104, and finally reached 106° just before death. The urine was normal except for a trace of albumin. The Wassermann reaction was negative. The blood urea was 22 mg. per 100 cc.

The *electrocardiogram* on the day of admission showed left axis deviation, slurring of the *Q-R-S* complex and low *T* waves in all leads. Three days later the voltage of the electrocardiogram was lower, the slurring of the *Q-R-S* was more marked, and the *T* wave in Lead IV became isoelectric. The clinical diagnosis was coronary thrombosis.

Autopsy (Dr. Bernheim, 10 hours after death). The heart weighed 500 gm. There was marked dilatation, particularly of the right auricle and right ventricle. The aortic cusps were rigid, calcific and markedly thickened. The right and posterior cusps were fused. There was marked narrowing of the aortic orifice. The coronary ostia were wide open, and the coronary arteries were patent throughout. There was a mucopurulent bronchitis and tracheitis. There was marked acute passive congestion of the viscera, a small hydrothorax, and ascites.

Comments. The first 4 cases illustrate the gradual development of the anginal syndrome with the progress of the aortic narrowing. In Case 1 the evolution of the symptoms paralleling the advancing valvular lesion is particularly striking. In this case, too, the autopsy revealed essentially normal coronary arteries.

On the basis of the prevalent theory that the anginal syndrome is caused by anoxemia or ischemia of the heart muscle, the mechanism in these cases is readily understandable. The blocking of the blood flow to the myocardium takes place at the aortic orifice instead of in the coronary arteries themselves. A casual inspection of some of these valves deformed by calcified nodules reveals how extreme this obstruction can be. Moreover, it impairs the blood supply in the territories of both the right and left coronary arteries simultaneously, in contrast to the more localized area of impeded blood flow usually occurring in coronary arteriosclerosis.

In Case 4 the anginal syndrome was always more accentuated when, as a result of the appearance of heart block, the heart rate dropped to 40. Because of the narrowed aortic orifice, the heart

could not compensate for this slowed rate by increasing the stroke volume, so that relative ischemia of the heart muscle occurred. I have seen analogous phenomena in patients with very tight mitral stenosis who felt very uncomfortable, with increased dyspnea and other evidences of heart failure, when the pulse became too slow. In one woman with sinoauricular block the heart rate often ranged between 40 and 46. During such a period she was very uncomfortable, and was relieved of many of her symptoms when the rate rose to 80 or 90. I have seen a number of patients with mitral stenosis and auricular fibrillation in whom evidences of congestive failure increased when the ventricular rate as a result of digitalis administration dropped to 50 or 60, and who improved when the rate again reached the neighborhood of 80, if there was no accompanying demand for increased work of the heart.

When the aortic orifice is greatly narrowed, rapidly developing heart failure by still further retarding the blood flow through the minute opening may induce an acute myocardial ischemia analogous to that following coronary artery thrombosis and giving rise to identical symptoms. This is dramatically illustrated by the sudden death of Case 1 following a shocking attack of precordial pain, and of Case 2 shortly after the abrupt onset of intense epigastric pain in the course of lobar pneumonia. In Case 6 the complete clinical picture of coronary thrombosis was simulated by advanced heart failure in the presence of a tight aortic stenosis.

Angina pectoris has often been noted in patients with aortic insufficiency, and since all of my patients had aortic insufficiency as well as stenosis it might be asserted that it was the incompetency, rather than the narrowing of the valve that was responsible for the cardiac pain. Heart pain in patients with aortic insufficiency is of two main types. In syphilitic aortic insufficiency the true anginal syndrome is common and is caused by the encroachment of the luetic lesion on the mouths of the coronary arteries, with resultant narrowing. There is rarely, if ever, stenosis of the aortic valve. More rarely paroxysmal cardiac pain is observed in young individuals with rheumatic aortic insufficiency.^{7,8} This is not a true Heberden's angina. The pain is not related to effort and is associated with marked vasomotor disturbances. Intense precordial pain which often radiates down one or both arms is accompanied by extreme throbbing of the heart and arteries, tremendous rise in blood pressure, and a rapid heart rate. The mechanism of these attacks is not clear, but it is certainly of a different nature than that of classical angina pectoris. In patients with calcareous aortic stenosis, neither of the above mechanism is called into play. It is significant that the calcific lesion does not extend up the sinuses of Valsalva to block the orifices of the coronary arteries.

Still less attention has been paid to the clinical manifestations of conduction defect in patients with aortic stenosis. Yet this associa-

tion too, while not as frequent as the anginal syndrome, is not uncommon. Its anatomic basis was established years ago by Mönckeberg, and has been well summarized by Uehlinger.⁹ The calcification commonly spreads from the aortic valves to the annulus fibrosus and to the interventricular septum, often impinging upon and destroying the auriculoventricular bundle. East¹⁰ recorded 2 cases in which the calcified masses had spread from the aortic valve down into the septum and had caused disturbances in conduction. Years ago, before the recognition of heart block, Parkes Weber,¹¹ described a patient with aortic stenosis and a pulse rate of 44. Allbutt¹² observed 2 similar patients, 1 with a pulse rate of 40 and the other 30. In Uehlinger's case a subacute bacterial endocarditis had been engrafted upon a calcific aortic-stenotic lesion, and the inflammatory reaction had invaded the bundle and produced heart block. A very similar case has been described by Lemierre and Rudolph.¹³ Campbell and Shackle¹⁴ observed a number of patients with aortic stenosis and bundle-branch block.

In the present series, Case 1 showed transient bundle-branch block, Case 5 had complete heart block, and Case 4 had intermittent heart block.

The etiology of the calcific lesion has given rise to much difference of opinion. The ages of our patients at the onset of the anginal syndrome were 35, 44, 42 and 56 years, respectively. The development of the lesion in early adult life militates against the view that it is caused by a degenerative process of senescence. Clawson¹⁵ has pointed out that in these patients the degree of senile arteriosclerosis of the aorta is less than in persons of similar age without this lesion, and has inferred from this that the injury to the aortic cusps begins early in life; for the narrowed aortic orifice protects the aorta from the usual forceful impact of the blood ejected with each systole. Clawson, too, noted a history of rheumatic infection in many of his cases, and concluded that the aortic calcific lesion was the end result of an infectious process. Christian¹⁶ holds a similar opinion. With this view I agree. The lesion seems to develop in individuals who have experienced a solitary, or even a subclinical rheumatic infection in childhood or in early life. The rheumatic process does not progress, but a gradual calcification of the injured valve takes place. Valvular deformity seems to favor more rapid development of atheroma and calcification.

Summary. The syndrome of angina pectoris is common in patients with aortic stenosis. It appears to be caused, not by disease of the coronary arteries, but by the narrowing of the aortic valvular opening itself, which impairs the blood supply to both coronary arteries simultaneously. Sudden heart failure in these patients is often followed by symptoms simulating coronary thrombosis.

Auriculoventricular conduction disturbances are also often associated with the calcific form of aortic stenosis. These are determined

by extension of the calcific process into the annulus fibrosus, or ventricular septum. At times a secondary infection of the diseased valve causes heart block by direct extension into the auriculo-ventricular bundle. Isolated aortic stenosis is probably of rheumatic origin.

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A COMPARATIVE STUDY OF THE GEOGRAPHIC DISTRIBUTION OF RHEUMATIC FEVER, SCARLET FEVER AND ACUTE GLOMERULONEPHRITIS IN NORTH AMERICA.

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ALTHOUGH certain epidemiologic studies on scarlet fever and rheumatic fever are available, comprehensive data on the geographic distribution of acute glomerulonephritis are lacking. This paper

presents a study of the incidence of acute glomerulonephritis in 24 hospitals in North America from 1910 through 1931. These data have been compared with the incidence of rheumatic fever in the same hospitals from 1910 through 1925. The statistics on the geographic frequency of scarlet fever compiled by Schroeder and Longacre¹ have been made available for comparative study.

Method of Obtaining Data. The method of obtaining the data for the incidence of rheumatic fever has been described in a previous paper.² In that study questionnaires were sent to a representative group of hospitals in North America for information as to the number of cases of rheumatic fever, number of medical admissions, and number of total admissions over a period of years. From the information thus obtained the conclusion was drawn that "the yearly admission rate for rheumatic fever in a selected series of hospitals in the United States and Canada is greater in the northern than in the southern regions of the continent."

In pursuance of limited studies on the etiology and mechanism of acute nephritis a similar questionnaire was sent to the same group of hospitals requesting information on the yearly incidence of acute nephritis. Adequate data were received from 24 hospitals.

It was obvious that the number of cases reported from each hospital would in part depend upon such factors as the presence or absence of pediatric or contagious services. Although no accurate correction could be made for this variable, it was found that the presence or absence of such services was uniform in the various geographical regions. In order to minimize inaccuracy, the yearly incidence of acute glomerulonephritis was always considered in terms of the yearly *medical admission rate*, rather than the *total admission rate*. By this method the recorded frequency of acute nephritis would not be influenced by the presence or absence of large obstetrical or surgical services in one hospital as compared with another.

In a number of instances the hospital statistics failed to give the medical admission rate over a number of years, although the total hospital admission rate was made available. The medical admission rate was, therefore, calculated on the basis of special information furnished by the respective hospitals. In some instances the medical admission rates obtained in this study failed to agree with the rates furnished in answer to the first questionnaire sent in 1926. In most cases the differences were negligible. In certain reports, however, the spread of the two figures was surprisingly large and the final accepted figure was determined on the basis of the known total admission rate.

It was realized that the diagnosis of acute glomerulonephritis might vary somewhat in the hospitals studied, but it was felt that the degree of error produced by the inclusion of cases of nephritis due to bichlorid of mercury poisoning, for example, would not be significant.

The statistics for the geographical distribution of scarlet fever have been compiled by Schroeder and Longacre from the United States Public Health Reports and forms a part of their accompanying paper.

Presentation of Data. The tables contain the data for rheumatic fever and scarlet fever from which the graph has been constructed. The incidence of these diseases over a period of years is shown for the four latitude areas selected. The figures for scarlet fever included in the accompanying paper are in terms of cases per 100,000 population from the years 1919 through 1931. The data for rheumatic fever and acute glomerulonephritis are derived from the same hos-

TABLE 1.—RHEUMATIC FEVER, ACUTE NEPHRITIS AND TOTAL ADMISSIONS TO MEDICAL WARDS IN 24 HOSPITALS IN THE UNITED STATES AND CANADA.*

	Good Samaritan, Portland, Ore.			Vancouver General, Vancouver, B. C.			Winnipeg General, Winnipeg, Man.			Royal Victoria, Montreal.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910										41	7	1363
1911										53	11	1475
1912										61	9	1496
1913										85	11	1548
1914										64	24	1545
1915										33	17	1477
1916										23	5	1425
1917				145	29	2051				22	18	2045
1918				23	26	2127				19	15	2662
1919				88	31	2793				20	20	1989
1920				114	50	3093				39	16	1931
1921				89	51	2102				27	10	1883
1922	38	14	2223	98	56	2367				26	5	2154
1923	27	17	2225	66	20	2098				36	14	2516
1924	28	19	2319	80	38	1940				31	11	2228
1925	44	9	2316	43	..	2203	130	13	2937	44	4	2434
1926		14	3182			4	2932	..	7	2518
1927		11	3146			10	3001	..	22	2601
1928		9	3650			20	3271	..	14	2884
1929		8	3545			5	3324	..	21	2916
1930		8	1956			6	3164	..	19	3006
1931		7	1647			6	3306	..	7	3205
Av. ratio	1:66	1:228		1:27	1:61		1:22	1:342		1:48	1:165	
	Montreal General, Montreal.			City, Cleveland.			Harper, Detroit.			Toronto General, Toronto.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910												
1911												
1912												
1913												
1914												
1915												
1916												
1917												
1918												
1919		9	1466									
1920	49	15	1647	..	58	1265	..	23	1739	..		
1921	40	14	1477	47	105	1216	..	10	1434	18	..	2333
1922	46	10	1463	26	34	1378	..	30	1561	20	..	2277
1923	24	7	1590	57	37	1315	9	30	1561	40	..	2883
1924	43	9	1325	63	40	1468	16	12	1400	55	..	2612
1925		4	1302	78	85	1905	10	5	1549	38	..	2674
1926		5	1363	..	41	2354	..	12	1311	..		
1927		5	1437	..	29	2339	..	10	1301	..	17	1854
1928		5	1577	..	29	2440	..	16	1566	..	18	2047
1929		6	1629	..	29	2274	..	10	2089	..	27	2275
1930		11	1596	..	38	2192	..	9	1967	..	13	2251
1931		8	1930	..	38	2315	..	9	1838	..	11	2249
Av. ratio	1:37	1:181		1:26	1:39		1:129	1:109		1:74	1:124	
	Presbyterian, New York.			Massachusetts General, Boston.			Peter Bent Brigham, Boston.			San Francisco, San Francisco.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910				60	4	2209		
1911				51	15	2508		
1912				76	14	2654		
1913				52	11	2511	..	4	694	..		
1914				27	8	2470	40	1	1744	..		
1915	42	..	1473	24	13	2735	36	10	1751	..		
1916	50	25	1807	31	24	2618	45	24	1952	..		
1917	55	24	1819	32	22	2487	35	20	1898	..		
1918	35	11	1798	37	11	2711	38	31	2369	..		
1919	50	15	2256	24	14	2462	22	15	2476	..	25	1482
1920	55	9	1897	19	15	2443	17	6	2463	29	23	1684
1921	60	12	1832	32	36	2679	20	8	2365	30	15	1657
1922	50	22	1827	40	16	2765	31	7	2668	32	20	1720
1923	67	17	1584	18	15	2570	30	9	2573	36	14	1636
1924	101	33	1704	34	15	2752	39	7	2331	34	33	2020
1925	104	18	1688	32	12	2790	48	6	2026	30	23	2155
1926	31	3093	..	6	2167	..	22	2111
1927	28	3290	..	13	2421	..	18	2314
1928	15	3408	..	11	2264	..	18	2356
1929	18	3260	..	2	2274	..		
1930	13	3047	..	10	1996	..		
1931	15	2980	..	5	1980	..		
Av. ratio	1:29	1:98		1:70	1:164		1:68	1:207		1:36	1:90	

* RF, yearly number of cases of rheumatic fever; AN, of acute glomerulonephritis; MA, of total admissions to the medical wards.

TABLE 1.—RHEUMATIC FEVER, ACUTE NEPHRITIS AND TOTAL ADMISSIONS TO MEDICAL WARDS IN 24 HOSPITALS IN THE UNITED STATES AND CANADA*—Continued.

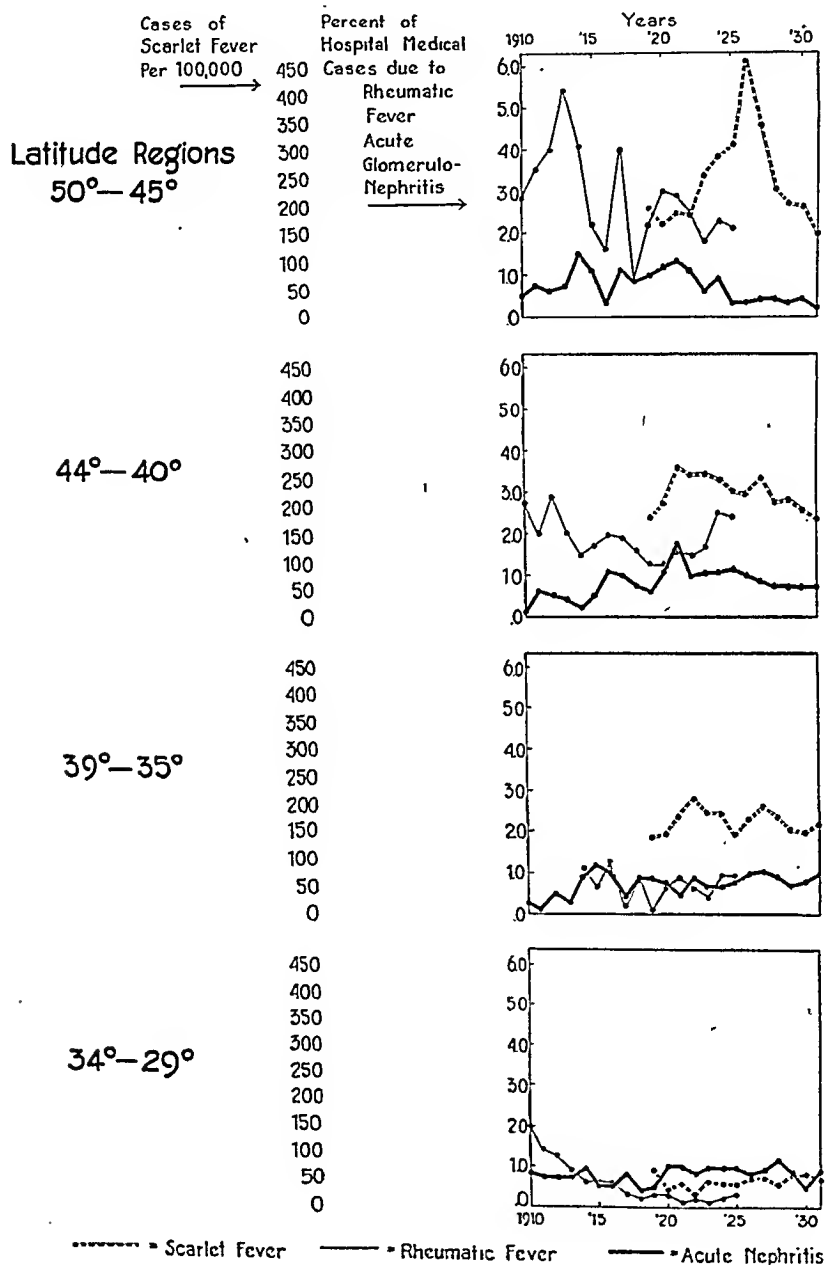
	Denver General, Denver.			State University, Oklahoma City.			Kansas City General, Kansas City, Mo.			City No. 2 (Col.), St. Louis.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920	2	9	1423	6	..	1210
1921	9	6	1546	7	..	1482
1922	1	13	1780	3	15	1788	8	..	1485
1923	2	8	1376	3	11	1849	0	..	2017
1924	19	16	1205	0	2	1463	9	12	1906	20	3	2584
1925	39	11	1181	0	1	1398	3	11	1916	18	2	2439
1926	8	569	..	10	1223	..	5	2144	..	36	2439
1927	13	714	..	8	1208	..	15	2390	..	42	2393
1928	12	940	..	24	1420	..	9	2622
1929	8	879	..	5	1456	..	5	2295	..	37	2735
1930	16	825	..	11	2076	..	8	2713	..	33	3216
1931	13	990	..	2	2130	..	6	2403	..	47	5210
Av. ratio	1:41	1:75		1:2006	1:184		1:359	1:223		1:190	1:105	

	Memphis General, Memphis, Tenn.			Baptist Memorial, Memphis, Tenn.			Louisville City, Louisville, Ky.			Johns Hopkins, Baltimore.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	5	1670
1911	2	1650
1912	9	1775
1913	6	1722
1914	19	14	1723
1915	10	21	1626
1916	22	17	1635
1917	5	8	1811
1918	17	17	1946
1919	2	6	2056
1920	2	..	1264	8	8	1941
1921	2	..	1285	21	9	1844
1922	10	20	1538	4	..	1452	19	9	1948
1923	4	16	2273	3	..	1705	9	12	1887
1924	10	5	1927	5	..	2030	27	..	1352	15	9	1814
1925	9	20	1872	2	..	1760	19	..	1177	34	24	1898
1926	13	1381	..	31	2277
1927	10	1338	..	34	2398	..	21	1392
1928	10	1681	..	37	2934	..	22	1500
1929	22	1807	..	16	3728	..	5	1773
1930	17	1718	..	19	2103	..	9	2024
1931	23	2212	..	36	1873	..	30	1929	..	30	2033
Av. ratio	1:230	1:113		1:527	1:88		1:55	1:99		1:122	1:150	

	Baylor, Dallas, Texas.			John Sealey, Galveston, Texas.			Charity, New Orleans.			Touro Infirmary, New Orleans.		
	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.	RF.	AN.	MA.
1910	3	564	91	39	4537
1911	3	725	67	38	4600
1912	806	65	38	5102
1913	5	654	49	39	5477
1914	3	842	41	68	6368
1915	0	1	1080	54	43	6720
1916	0	3	1061	49	39	6765
1917	0	7	1031	32	63	7637
1918	0	4	1510	24	39	8553
1919	0	8	1691	0	5	875	26	34	6025
1920	2	11	1983	1	6	908	23	76	5181
1921	2	10	1516	0	13	807	7	56	5332
1922	1	6	1645	2	8	892	15	48	5042
1923	1	11	1936	1	27	805	9	49	5842
1924	5	12	2173	1	35	904	21	59	6805	2	16	1334
1925	9	9	2423	4	20	976	32	62	7620	2	36	1598
1926	4	1385	..	14	1132	19	1670
1927	6	1189	..	8	982	23	1590
1928	8	1044	..	4	977	36	1899
1929	9	1696	..	9	931	20	1826
1930	2	1511	..	8	840	13	1740
1931	7	1878	..	8	938	25	1326
Av. ratio	1:668	1:214		1:1203	1:100		1:161	1:122		1:733	1:69	

* RF, yearly number of cases of rheumatic fever; AN, of acute glomerulonephritis; MA, of total admissions to the medical wards.

pitals and consist of the total number of cases reported by the hospitals in each latitude group for each year, and the total number of medical admissions for that same year. The graph shows that the



case frequency of scarlet fever diminishes from latitude region 50-45 degrees to latitude region 34-29 degrees. A similar diminution in frequency exists for the hospital medical admission rate for

rheumatic fever. In contrast to this fact, the hospital medical admission rate for acute nephritis is relatively uniform in the four latitude regions studied.

Comment. The majority opinion at present is that the etiologic agent in scarlet fever is the hemolytic streptococcus. Increasing evidence³ suggests that the hemolytic streptococcus plays an important rôle in the mechanism of rheumatic fever. The clinical and biologic studies of many workers, notably Longcope⁴ and his associates, would ascribe a chief etiologic rôle in acute nephritis to the hemolytic streptococcus. Additional evidence in favor of this concept is found in the observation by Seegal and Lyttle⁵ that 20 out of 22 consecutive cases of acute glomerulonephritis studied in New York City showed a significantly high titer of a hemolytic streptococcus antibody termed antistreptolysin by Todd.⁶

It is of interest, therefore, to note the variation in the geographic distribution of these diseases on the basis of the limited statistics available for this study. No explanation is at hand as yet to account for the failure of the hospital incidence of acute glomerulonephritis to follow the type of geographic distribution illustrated by the curves of the two other diseases studied.

Owing to the possibility that agents other than the hemolytic streptococcus may have been responsible for the frequency of cases of acute glomerulonephritis in the southern hospitals, a special study was undertaken to determine this point. The conclusions drawn from the unpublished observations show that much the same type of preceding infection, initiated by the hemolytic streptococcus, occurs in the southern as in the northern patient with acute glomerulonephritis.

Summary. 1. A comparative study has been made of the geographic distribution in North America of acute glomerulonephritis, rheumatic fever and scarlet fever.

2. The case rate for scarlet fever diminishes progressively from latitude region 50-45 degrees to 34-29 degrees.

3. The yearly hospital medical admission rate for rheumatic fever in 24 hospitals shows a similar decrease in the same latitude regions.

4. In contrast to the diminished case frequency of scarlet fever and rheumatic fever in southern latitudes as compared to northern latitudes, the yearly hospital medical admission rate for acute glomerulonephritis does not vary significantly in the four latitude regions studied.

5. The failure of acute glomerulonephritis to diminish in frequency in southern latitudes might be interpreted as supporting the hypothesis that agents other than the hemolytic streptococcus play the chief etiologic rôle in this disease. This does not seem likely, however, since considerable evidence is available incriminating the hemolytic streptococcus as the main incitant of the disease.

6. Since evidence is available ascribing etiologic significance to the hemolytic streptococcus in all three diseases studied here, the variation in the geographic distribution of these diseases based upon the limited data presents a problem in specific host and bacterial interaction.

We wish to express our gratitude to the administrative and medical staffs of the many hospitals that have generously contributed the data upon which much of this study is based.

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ISOLATED TRICUSPID STENOSIS OF PROBABLE RHEUMATIC ORIGIN.

REPORT OF A CASE WITH UNUSUAL CLINICAL AND PATHOLOGICAL FINDINGS.

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STENOSIS of the tricuspid valve is by far the most infrequent of valvular lesions and, according to a very comprehensive review of the literature by Zeisler¹ in June, 1933, there have been only about 250 cases of acquired tricuspid stenosis reported to date. In view of this rarity the following case is presented.

Case Report. H. C., a white female, aged 24, single, was admitted September 1, 1934, to this hospital on the medical service of Dr. Henry Schumer, with the clinical diagnosis of acute cardiac decompensation, mitral stenosis, pulmonary edema and vasomotor collapse.

Family History. Negative for heart disease and tuberculosis.

Past Personal History. Negative for rheumatic fever or any of its manifestations, scarlet fever or other of the acute infections. She had always been pale and sickly as a child, had had a poor appetite, but repeated physical examinations were negative. There was no evidence of cyanosis in childhood and no dyspnea on exertion, but the patient complained of tiring easily.

Present Illness. This dates back to 8 years before admission. While swimming, patient suddenly became weak and cyanotic and had a slight

bloody expectoration. She was confined to bed for several weeks and parents at this time were told that she had a heart murmur. Following this there was noted cyanosis of the lips on exertion. This progressively increased and she also had frequent attacks of hemoptysis, the amount of blood varying from a few drops to a tablespoonful. There was no constant cough. Her general condition was fairly good until about 2 years ago when she developed congestion of the lungs. There was evidence at this time of cardiac decompensation from which she recovered. Since then she had been practically bedridden. One year ago she developed marked edema of the lower extremities with slight swelling of the face and neck. This condition cleared up with rest in bed.

On the day before admission the patient became extremely cyanotic and orthopneic and exhibited signs of peripheral circulatory failure. The pulse was imperceptible and the arterial blood pressure was not obtainable. On admission the heart sounds were distant, irregular and rapid. A soft pre-systolic murmur was heard over the entire precordium, being loudest over the mitral area and a pre-systolic thrill was felt over a corresponding region. Many sibilant and sonorous râles were heard at both bases of the lung. The cervical veins did not pulsate. The abdomen was distended and a fluid wave was obtained. The liver edge was felt two finger breadths below the costal margin, but did not pulsate. The extremities were cold and clammy and there was no edema. The leukocyte count was 20,400, of which 66% were mature granulocytes and 15% young or band forms. In view of her moribund condition, additional laboratory tests were not done, nor was a Roentgen ray taken. The cyanosis and dyspnea increased, the patient became anuric, developed Cheyne-Stokes' respiration with a gallop rhythm and expired the day after admission.

Relevant Postmortem Findings. A somewhat frail figure of fair nourishment, with marked cyanosis. The gross anatomic findings were: 1, Tricuspid stenosis; 2, mitral insufficiency; 3, chronic adhesive pericarditis; 4, hydropericardium; 5, subepicardial hemorrhages; 6, subendocardial degeneration; 7, advanced sclerosis of the lesser circulation; 8, ulcerative plaques in the pulmonary arteries; 9, chronic pulmonary tuberculosis; 10, cirrhosis of the liver; 11, hemangioma of the liver; 12, congested spleen; 13, exaggerated duodenal band; 14, cortical cyst of the right kidney; 15, ascites.

Heart. The pericardial sac was adherent to the dome of the diaphragm posteriorly. There was about 100 cc. of straw-colored fluid in the pericardial cavity. The heart itself was normal in position and measured 11 by 11 cm. in its greatest diameters. There were a few subepicardial hemorrhages noted, these being most prominent in the region of the auriculo-ventricular sulcus. The musculature was of normal color. There were no gross lesions in the papillary muscles, chordæ tendineæ or columnæ carneæ. The tricuspid valve, when viewed from its auricular aspect, was funnel-shaped. Its walls were smooth and it opened into the ventricle by an elliptical, smooth orifice, which measured 6 mm. in its longest diameter. The walls were somewhat thickened and inelastic, but there was no evidence of scarring or of chronic or recent vegetations (Fig. 1). Because of the non-pliability of the walls of the tricuspid valve, it was believed to be incompetent as well as stenotic. Histologically, there was marked fibrosis with some myxomatous degeneration and areas of vascularization, but no cellular exudate or signs of an active process (Fig. 2). The right auricle showed but a slight degree of hypertrophy and dilatation. The pulmonary valve showed slight atheromatous changes of the valve margins. The mitral valve was dilated and apparently insufficient, admitting 4 fingers, and there was slight sclerosis of the leaflets, especially of the more posterior one, but there was no evidence of stenosis. The aortic valve showed a marked degree of atheromatous change, extending for a few centimeters into the arch with

no evidence of stenosis. The left auricle exhibited marked hypertrophy and dilatation, especially the latter, measuring 9 by 6 cm. when the walls were distended. The auricular musculature was markedly fasciculated.

Serial sections of the myocardium to determine whether Aschoff bodies were present showed them in the wall of the left ventricle (Fig. 3). These consisted of a submiliary accumulation of large mononuclear cells, resembling plasma cells, both morphologically and in their staining qualities, together with some lymphoid cells. These were distributed in a spindle-shaped arrangement usually about the wall of a small radicle of the coronaries, most commonly found in the musculature of the left auricle and about the coronary vessels in the auriculoventricular sinus. Similar lesions were also found in other organs of the body.



FIG. 1.—Arrow points to the auricular aspect of the stenotic lesion present at the tricuspid orifice.

Lungs. There were several submiliary calcified areas in the region of the right apex which on section showed healed peribronchial tuberculosis. There was bronchopneumonia at both bases.

The pulmonary artery showed marked sclerosis in all of its radicles with advanced atheromatous changes in the larger vessels (Fig. 4). There was an area of beginning necrosis near the division of the main artery on the right side upon which was superimposed a recent adherent 2 cm. thrombus. There was an ulcerated ovoid area, 3 by 2 cm., at the point of division of the left main artery (Fig. 5). There was no discernible sclerosis in the greater circulation.

Liver. In spite of its apparent enlargement clinically, the liver was definitely smaller than normal, being contracted, firm and nodular and measured 20 by 14 cm. in its largest diameters. There was a small dark bluish circumscribed hemangioma on the anterior surface, near the inferior



FIG. 4.—Cut surface of pulmonary tissue showing extreme vascular sclerosis, the mouths of the vessels projecting prominently.



FIG. 5.—Ulcerated plaque in the left main pulmonary artery near its bifurcation.



FIG. 2.—Section through the tricuspid valve showing marked fibrosis with some myxomatous degeneration and areas of vasularization.



FIG. 3.—Aschoff lesion in the wall of the left ventricle.

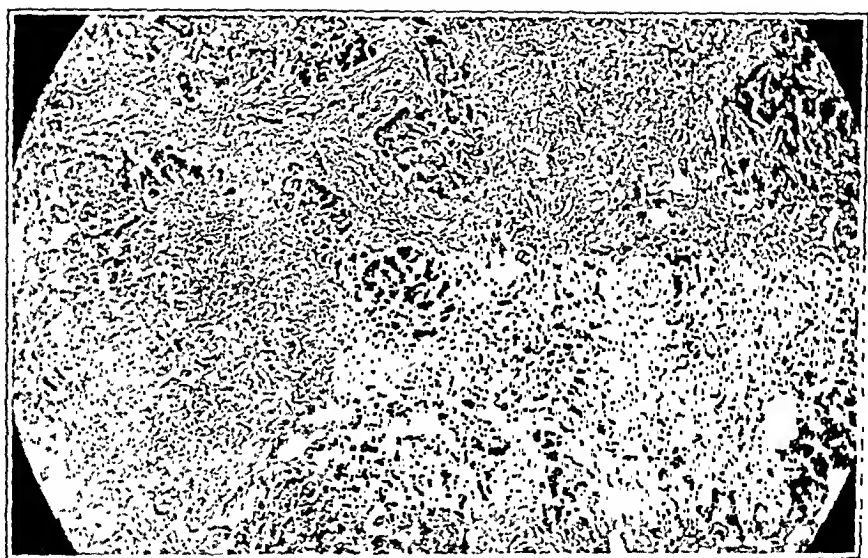


FIG. 6.—Section of liver showing extensive cirrhosis. Only scattered islands of atrophic liver parenchyma remain intact.

border of the right lobe, measuring 8 mm. in diameter and extending for about 3 mm. into its substance. On section, the liver showed an extreme degree of cirrhosis, spreading diffusely throughout the lobules. Microscopically, there was marked periportal cirrhosis with congestion about the central veins (Fig. 6). The hepatic veins were dilated. There were about 2000 cc. of thin serosanguinous fluid free in the peritoneal cavity.

Discussion of Tricuspid Stenosis. *Degree of Stenosis.* The circumference of the adult tricuspid ostium varies normally between 10 and 12 cm. according to White,² and this valve is regarded as stenotic if its orifice measures 8 cm. or less. Usually, the stenosis is not present to a marked degree. Functionally, the right heart, including its auriculoventricular valve, is relatively passive and may be considered as an adjuvant of the venous system. The pressure normally exerted on the tricuspid valve is low as compared to that on the mitral valve which is subjected to the stress and strain of the much more active left heart. Kerr and Morrison³ offer as an additional explanation for the relatively slight degree of stenosis seen in the tricuspid valve, the triangular shape which prevents its narrowing to the degree seen in mitral stenosis.

Of 30 cases reported by Dressler and Fischer,⁴ only 5 showed marked stenosis while their most advanced case barely admitted the passage of the small finger (approximately 1 cm. in diameter). Cottin and Saloz⁵ reported a case closely resembling ours anatomically in which a similar degree of stenosis was present. Oigaard⁶ described his case as admitting the passage of a pencil (approximately 7 to 8 mm.). The majority of reported cases had a much lesser degree of stenosis; thus Zeisler¹ gives 7.1 cm. as the circumference of the ostium in his case.

Association with Other Valvular Defects. Tricuspid stenosis is rarely a solitary lesion. Of 195 cases compiled by Fletcher,⁷ in only 14 cases was the tricuspid valve the only one involved while in 104 cases both the tricuspid and mitral were affected. In such instances, the narrowing of the mitral is usually the much more pronounced of the two. This has been the usual finding in other reported series. There may be associated lesions in the other two valves, the common picture being termed "Dreistienstenose," indicating a combined stenosis of the tricuspid, mitral and aortic valves. In a large percentage of cases, there is a relative, if not actual, tricuspid insufficiency associated with the stenosis as a result of the inability of the stenotic leaflets to approximate each other.

Etiology. The etiology of this condition has been the subject of a great deal of study and investigation. The belief was held formerly that most cases, if not all, were congenital in origin. Careful anamneses have revealed the incorrectness of this belief and now the consensus of opinion is that the great majority are acquired in postnatal life. In many instances no definite etiologic factor can be traced in the history and the appearance of cardiac

symptoms may be the first indication of the presence of a valvular lesion, but this does not imply that the patient was born with a damaged valve. This is emphasized very definitely in our case. Oigaard⁶ states that in more than one-half of the cases no etiologic factor is determinable. A congenital lesion usually manifests itself in infancy or early childhood. There is obtainable in such instances a history of cyanosis very early in life and postmortem examination of the heart will often disclose other congenital lesions such as pulmonary stenosis, narrowing of the aorta or defect of the interventricular septum.

In many cases there is present a history of acute articular rheumatism, repeated sore throat, chorea, muscular rheumatism ("growing pains") or other manifestations of a rheumatic affection. Cabot⁸ has stressed rheumatic heart disease without a history of so-called rheumatism. Aschoff bodies have been found in the hearts of patients in whom a history of attacks of articular rheumatism was not obtained. Other acute infections such as scarlet fever, typhoid fever and puerperal sepsis may be the inciting causes. An apparently truly congenital case has been reported by Cottin and Saloz⁵ where cyanosis appeared very early in infancy, became more pronounced as the child grew older with development of clubbing of the fingers. An antemortem diagnosis of tricuspid stenosis was made, based on classical physical findings and this was substantiated at necropsy. In their discussion, these authors differentiate between a congenital malformation of the valve and fetal endocarditis and conclude that the latter is the more plausible explanation in their case.

Often the macroscopic appearance of the valve makes one suspect a congenital origin when the valve edges are smooth and grossly resemble a malformation without the irregular appearance of cicatrization that we usually see following endocarditis. However, it is only when there is no history of predisposing infection, when cyanosis appears early in life, when serial sections of the myocardium fail to show the presence of Aschoff bodies, and especially if there are present other lesions that are usually considered congenital that the diagnosis of a congenital lesion can be made.

Our first impression on examining the tricuspid valve was that we were dealing with a congenital lesion that had gone unrecognized for a long time and had only become clinically evident after an acute illness. The complete absence of a history of rheumatic infection or other possible etiologic factors, together with the smooth appearance of the valve walls that showed no evidence of leaflets, nor of inflammatory reaction and resembled grossly a malformation, strongly suggested a prenatal affection. On the other hand, there were no other congenital deformities, nor was there present a history of cyanosis during infancy. The finding of Aschoff bodies

made a rheumatic cause for the valve lesion the most likely, even though it showed no active signs postmortem.

Other unusual features of this case were the absence of pulsation of the cervical veins, the relatively normal size of the right auricle and the sclerosis of the lesser circulation. We shall not enter into a discussion in this presentation of sclerosis of the lesser circulation of which we have apparently an example, but we believe that the two conditions are independent and cannot be explained on a single clinicopathologic basis. There was no evidence, microscopically, that the sclerosis was rheumatic in origin. The clinical picture was at no time characteristic and in this particular case, it seems impossible to have made a diagnosis of tricuspid stenosis before death. However, this condition should be borne in mind and suspected, especially in cases of rheumatic heart disease where the physical signs are localized to the region of the xiphoid process of the sternum.

Thus we have here an example of a rheumatic lesion involving principally one valve and not preceded by the usual symptoms which we have been accustomed to call rheumatism. The pallor, fatigability, anorexia and weakness of the patient as a child were probably rheumatic manifestations, as brought out recently by Kaiser⁹ and termed by him "minor rheumatic manifestations." The disease left its imprint on the heart musculature in the form of rheumatic nodules or Aschoff bodies, and on the tricuspid valve, causing extreme stenosis.

The small, nonpulsating liver was another surprising and unusual feature of this case, but some light was thrown on this by the gross and microscopic appearance of this organ, the cirrhosis being so marked in degree that it caused a contracture of the liver parenchyma, especially in region of the portal spaces and prevented stasis of blood in the radicles of the portal vein.

Summary. The case of tricuspid stenosis reported presents the following noteworthy features:

1. The extreme degree of narrowing of the tricuspid ostium, resulting in a valve grossly resembling a malformation rather than the end result of an inflammatory process.
2. The absence of involvement of the other valves, except for a mitral insufficiency and slight sclerosis.
3. The absence of an etiologic factor in the history, except for so-called minor rheumatic manifestations.
4. The finding of Aschoff bodies in the myocardium indicating the presence of rheumatic heart disease.
5. The indistinguishability clinically from mitral stenosis.
6. The absence of a pulsating liver and distention of the cervical veins.
7. The slight enlargement of the right auricle in face of the extreme stenosis.

8. The finding of advanced lesser circulation sclerosis, apparently an independent lesion.

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VARIABILITY OF MURMURS IN MITRAL STENOSIS.

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MITRAL stenosis was first mentioned in the literature by Mayow⁸ in 1669. The first definite knowledge concerning it appeared in 1715 in Vieussens¹⁴ treatise on the heart. No mention of cardiac murmurs is found in the first comprehensive textbook on heart disease written by De Senac.⁵ Corvisart³ described the palpable thrill of mitral stenosis in 1806. In 1826 Laennec¹⁰ first described the murmurs of mitral stenosis, one, as a dull bruit quite like the sound produced by a file rubbing on wood, and followed by a loud bruit somewhat rough and harsh. Hope⁹ first noted the variability of the murmurs when he described bruits audible in slow and rapid hearts with mild to severely stenosed mitral valves. He designated this rasping bruit as a diastolic murmur. Bertin¹ confirmed Laennec's descriptions of the murmurs, and further suggested that two distinct bruits were audible. Williams¹⁶ modified Hope's description of the murmurs, but also classified it as being diastolic in the cardiac cycle. Bouillaud² established the relationship of rheumatic fever to mitral stenosis; this had been mentioned by Pitcairn in 1788 and by Corvisart in 1806. Fauvel⁶ called the murmur presystolic, but added that this was not a positive sign of mitral stenosis. The tradition of a presystolic murmur essential

to the diagnosis of mitral stenosis persisted for many decades. In the second Herter Lecture in 1914, Lewis¹² stated that the murmurs which accompany mitral stenosis in different patients are very variable in their time relations and that they not only vary also greatly from cycle to cycle in the same patient but even vary both in time and quality. Crummer⁴ simply stated that no single murmur is constant or characteristic of mitral stenosis. White¹⁵ indicated that if we should rely on the presence of a presystolic murmur for a diagnosis of mitral stenosis we should miss at least half the cases of this valvular lesion.

This study indicates the importance of the variability of the murmurs in 237 cases of mitral stenosis. These 237 patients constituted 14.4% of a larger group of 1646 adults with organic heart disease seen in the Cook County Hospital.⁷ None of the patients in this report had any evidence of aortic insufficiency, hypertension, or thyrotoxicosis. Their ages varied from 15 to 68 years; 80% were 20 to 50 years old; the largest group (35.4%) was 31 to 40 years old. Auricular fibrillation was present in 110 patients (46.6%).

The murmurs were recorded to indicate the time in the cardiac cycle where each appeared best sustained. Six different groups were noted, which included, according to their frequency, the following: systolic-diastolic, systolic, presystolic-systolic, no murmurs audible, diastolic, and presystolic murmurs.

Systolic-diastolic Murmurs. These were audible in 159 (67.08%) of the 237 cases. The loud, rasping to-and-fro murmurs occupied the entire cardiac cycle. The bruits were most often localized to a small area surrounding the apex of the heart, but occasionally were audible over the whole precordium. Seventy-three (46%) of the 159 patients had auricular fibrillation and the characteristic rasping sound of the murmurs was unchanged. The exact timing of the murmurs was difficult, due to the rapid cardiac rate and the frequent changes in the irregularity. These were designated systolic-diastolic murmurs because the bruits were the longest, loudest and harshest of all the murmurs noted.

Systolic Murmur. The systolic murmur was present alone in 36 cases (15.2%), of which 23 (64%) had auricular fibrillation. This murmur was audible over the entire precordium in all 36 patients. The bruit was loud and intense in each instance.

Presystolic-systolic Murmurs. Twenty-eight patients (11.8%) presented a short, loud, rasping, crescendo murmur followed by a long, loud, clear bruit. The rhythm was regular in 24 and auricular fibrillation was present in the other 4 patients.

No Murmurs Audible. Eight patients (3.37%) with auricular fibrillation were in this group. The heart was auscultated frequently, but in each case no murmur was discernible. Lewis¹³ emphasized this when he stated that in auricular fibrillation, mitral stenosis may be concealed, the heart at times presenting no murmurs.

TABLE 1.—MURMURS IN THE 237 CASES OF MITRAL STENOSIS.

	Cases.	White male.		White female.		Colored male.		Colored female.		Totals.	
		R.*	AF.†	R.	AF.	R.	AF.	R.	AF.	R.	AF.
1. Systolic-diastolic	159 (67.08%)	43	39	22	33	10	0	11	1	86	73
2. Systolic	36 (15.3%)	6	13	4	9	1	0	2	1	13	23
3. Presystolic-systolic	28 (11.8%)	11	3	4	1	6	0	3	0	24	4
4. No murmurs	8 (3.3%)	0	5	0	2	0	0	0	1	0	8
5. Diastolic	3 (1.26%)	1	1	0	1	0	0	0	0	1	2
6. Presystolic	3 (1.26%)	1	0	2	0	0	0	0	0	3	0
Totals	237 (100%)	62	61	32	46	17	0	16	3	127	110
		123		78		17		19		237	
		84.8%				15.2%				100%	

* Regular rhythm.

† Auricular fibrillation.

Diastolic Murmur. This short rasping murmur was audible in 3 cases (1.26%); 2 had auricular fibrillation.

Presystolic Murmur. This bruit occurred with the same frequency as the diastolic murmur. The cardiac rate and rhythm were regular in each case. The diastolic and presystolic murmurs of mitral stenosis occurred alone only 6 times (2.52%) in this group of 237 patients. The rarity was surprising as compared with the teachings prevalent concerning the characteristic murmurs of mitral stenosis.

Comment. There were 76 deaths (32%) during the period of this study. The murmurs audible had no apparent relation to the mortality. Auricular fibrillation also seemed to have little influence on the outcome. Of the 110 patients with auricular fibrillation, the frequency with which the murmurs occurred was approximately the same as in those with regular sinus rhythm. In these cases the murmurs and the frequency of their occurrence was as follows: Systolic-diastolic, 66.3%; systolic, 20.9%; presystolic-systolic, 3%, and diastolic, 1.8%. The other 8 (7.2%) were the patients with no murmurs audible. Auricular fibrillation was infrequent in the colored patients with mitral stenosis. Of the 36 colored patients, 17 males and 19 females, auricular fibrillation occurred in 3 of the females and not at all in the males.

The incidence of double murmurs, systolic-diastolic and presys-

toxic-systolic, was 79%. All of the murmurs mentioned, whether single or double, were immediately recognized by the characteristic rasping sound, audible even to the untrained ear. The loud systolic murmur was present alone in 15.2%. The combination of auricular fibrillation and a loud systolic murmur audible over the entire precordium, in the absence of thyrotoxicosis or hypertension, was evidence of mitral stenosis. Levine¹¹ stated that loud systolic murmurs are always associated with cardiovascular disease. Lewis¹³ advised that less effort be expended on learning to time the murmurs of mitral stenosis and more energy be applied to recognizing the characteristic sound, like knowing the bark of a dog. The marked variability of the murmurs of mitral stenosis, as noted in the literature and as indicated in this study, suggest the general acceptance of this advice.

Summary. 1. The variability of the murmurs in 237 cases of mitral stenosis is reported.

2. Auricular fibrillation was present in 46.6%; it had no effect on the character or type of murmurs audible.

3. Double murmurs were found in 79%.

4. Systolic murmurs alone were present in 15.2%.

5. The murmurs of mitral stenosis were readily recognized by the characteristic rasping sound without resorting to definitely isolating the murmurs in the cardiac cycle by timing.

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THE VALUE OF COLLOIDAL SULPHUR IN THE TREATMENT OF CHRONIC ARTHRITIS.

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SULPHUR in one form or another has been used as a therapeutic agent since ancient times. Only recently, however, has its value in the treatment of chronic arthritis been stressed. Among the earliest papers on the use of colloidal sulphur in the treatment of chronic arthritis are those of Comrie¹ and Cawadias,² both of whom report favorable results. In 1927, Race³ reported favorably on its use in 42 cases treated in the Devonshire Hospital. More recently, the study of the effect of sulphur has been given further impetus. Wheeldon and Main⁴ report that, on the basis of 250 cases studied for 2 years, they were convinced that colloidal sulphur had a definite place in the therapeutics of arthritis. Woldenberg,⁵ employing colloidal sulphur in the treatment of 100 cases of atrophic arthritis, believed that it had a definite therapeutic value. Senturia⁶ reported improvement in 75% of 60 cases, 43 of which were hypertrophic, the rest being either atrophic or mixed types or fibrositis. Sullivan and Hess⁷ and Loeper and his associates⁸ report good results in a smaller series of cases.

Sulphur metabolism does not come within the scope of this paper, but it should be pointed out that the cystin content of certain structures is considered a reliable guide to the sulphur metabolism of the body. Sullivan⁹ recently described a method for estimating the cystin content of the finger nails. Sullivan and Hess,⁷ in a study of the finger nails of 105 patients with arthritis, found the cystin content below normal in 65% of the cases. An editorial in the *Lancet*¹⁰ recently mentioned that Neligan reported he found a low cystin content of the finger nails in 75% of his cases.

Sullivan and Hess⁷ applied sulphur therapy to 6 patients with a subnormal cystin content of the finger nails and found that improvement was accompanied by a rise in the cystin content of the finger nails. Woldenberg⁵ also reported an increase in the cystin content of the finger nails after colloidal sulphur therapy.

The present study was undertaken not only to evaluate the clinical results of colloidal sulphur therapy in chronic arthritis and its effect

upon certain cellular and immune reactions of the blood, but to ascertain the effect of this form of therapy upon the cystin content of the finger nails and to determine whether the cystin determination is of value in selecting cases for sulphur therapy.

The patients were selected on admission to the clinic without regard to type, severity, age, or duration of symptoms. The usual routine physical and laboratory examinations were made on all patients and the cystin content of the finger nails was estimated according to the method of Sullivan⁹ before treatment was instituted. The blood studies included non-filament cell counts, sedimentation rates using Westergren's technique, and red and white blood cell counts. They were also made at varying intervals after treatment. The clinical symptoms were recorded on special charts.¹¹

An aqueous solution of colloidal sulphur (Sulisocol) containing 10 mg. per cc. was administered intravenously or intramuscularly twice weekly. No other treatment was given. Since the usual dosage (10 mg. twice weekly) did not produce definite effects, it was increased to 20 mg. twice weekly. In those cases where no improvement was obtained with 20 mg. doses, it was further increased to a maximum of 30 mg. twice weekly. Certain patients who received 10 mg. twice weekly for several weeks and who were not improved were definitely improved when the dose was increased to 20 or 30 mg. A few patients could not tolerate the larger doses.

Symptoms of fatigue, drowsiness, loss of appetite, headaches and increased pain, stiffness or swelling of the joints after the intravenous injection of colloidal sulphur indicate overdosage. In such instances the dose should be reduced but, if the symptoms still persist with the smaller dosage, the intramuscular method should be used instead. If this does not relieve the symptoms, the use of colloidal sulphur should be discontinued. As with vaccine therapy, the optimum dose is characteristic for each individual.

Toxicity. Of 200 patients with arthritis of different types treated with colloidal sulphur during the past 18 months, only a few had severe symptoms of toxicity and they were temporary. A few developed urticaria and scarlatiniform eruptions but these quickly subsided when the medication was discontinued. Some complained of nausea and an occasional patient complained of vomiting, abdominal cramps and diarrhea. Others complained of severe fatigue, headache, drowsiness, heaviness of the eyes, extreme nervousness, generalized muscle soreness and occasionally of insomnia and loss of appetite. A few patients receiving 30 mg. doses had chills and fever which appeared 2 to 4 hours after the injection and they were confined to bed for 24 hours. These reactions did not occur during the first 3 or 4 weeks of treatment. It was concluded, therefore, that these patients had been given an excess of sulphur and that this had caused the reaction. Patients receiving 10 or 20 mg. did not experience reactions of this type. Untoward reactions following

the intravenous administration of sulphur were reduced or were entirely eliminated when it was given intramuscularly. Intramuscular injections did not produce pain, soreness or local reactions. Any symptoms of toxicity quickly disappeared when the medication was terminated.

Controls. Twenty-five patients, consisting of 10 with mixed arthritis, 8 with rheumatoid arthritis and 7 with osteoarthritis, were used for control purposes. Ringer's solution was administered intravenously as placebo medication for from 6 to 8 weeks. This was followed by the intravenous injection of sulphur for the same length of time. Sedimentation rates, non-filament cell counts and red and white blood cell counts were made before, during and at the end of both the control and the test periods.

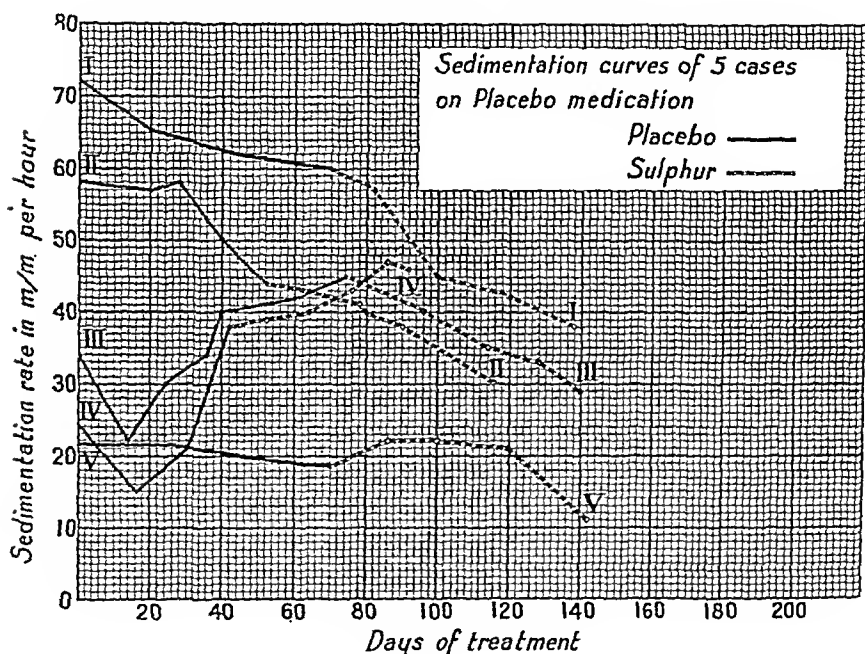


FIG. 1.

With patients receiving placebo medication the mean sedimentation rate was 22.22 mm. before and 21.21 mm. after treatment and the mean non-filament cell count was 15.35% before and 15.12% after treatment. With those patients given colloidal sulphur therapy, the mean sedimentation rate was 23.5 mm. before and 16.9 mm. after treatment and the mean non-filament cell count was 16.12% before and 13.9% after treatment. Although there was only a slight difference between the mean initial and final sedimentation rates and non-filament cell counts following placebo medication, the individual differences were marked. The mean trends were

practically unchanged with placebo medication. Figure 1 illustrates graphically the sedimentation rates of 5 typical cases.

With sulphur therapy the reduction in the sedimentation rate and non-filament cell count was comparatively slight but this was regarded as significant because the initial readings were low.

The Effect of Sulphur Medication Upon the Cystin Content of the Finger Nails. The normal cystin content of the finger nails was considered to be 12 mg. or above per 100 mg. of nails. Twenty-five patients with a subnormal cystin content were studied to determine the quantitative effect of intravenous colloidal sulphur. These

TABLE 1.—THE EFFECT OF INTRAVENOUS SULPHUR THERAPY UPON THE CYSTIN CONTENT OF THE FINGER NAILS.

Case No.	No. of injections	Total mg. of sulphur injected.	Period of treatment (days).	Cystin content in mg. per 100 mg. of nails.		Clinical results.
				Initial.	Final.	
6226-33	27	540	171	7.27	14.28	Improved.
1177-34	10	200	112	7.37	9.73	Improved.
21642	9	110	131	7.88	12.82	Improved.
147-34	15	300	78	8.07	12.18	Unimproved.
14044-33	13	250	151	8.60	12.95	Unimproved.
22674-33	13	250	73	8.96	15.61	Improved.
5380-34	10	200	78	8.98	11.36	Improved.
1816-33	10	200	116	9.74	13.51	Unimproved.
2172	21	310	97	9.82	11.02	Improved.
28465-33	13	260	140	9.88	12.38	Improved.
15645-33	9	90	47	10.33	13.88	Improved.
13356-34	12	240	206	10.37	11.59	Unimproved.
199-34	9	180	78	10.41	12.50	Improved.
2027-34	16	320	72	10.41	11.31	Improved.
19464-33	30	450	170	10.68	13.44	Improved.
11921-34	12	270	117	10.68	12.13	Improved.
1338-34	45	900	193	10.73	14.00	Improved.
12695	18	180	152	10.84	10.87	Unimproved.
13323-34	10	200	81	11.09	12.64	Unimproved.
18097-34	12	220	77	11.11	14.34	Improved.
23918-33	22	300	103	11.30	12.44	Unimproved.
10256-34	17	320	141	11.62	13.00	Improved.
7829	16	340	113	11.80	12.37	Unimproved.
11917-34	22	530	126	11.84	12.50	Unimproved.
17362-34	35	620	144	11.90	12.50	Improved.

patients received a mean of 310.2 mg. of colloidal sulphur over a mean period of 119.56 days. The mean cystin content was 10.07 mg. before and 12.65 mg. per 100 mg. of finger nails after sulphur medication, a mean increase of 2.58 mg. per patient (Table 1). In 21 cases there was a definite increase in the cystin content but in the other 4, it was less than 1 mg. A difference of 1 mg. was not considered an increase because of the possibility that it might be due to experimental error, etc.

An Analysis of the Effects of the Intravenous Administration of Sulphur in 100 Cases. The classification of arthritis described in a previous paper¹¹ was used in the present study. The 100 cases studied are grouped according to the cystin content of the finger nails and the percentage of improvement in each group considered

separately (Table 2). The criteria of improvement were: 1, improvement in focal symptoms, *e. g.*, reduction of pain, swelling, stiffness, etc.; 2, improvement in constitutional symptoms, *e. g.*, gain in weight, lessening of fatigue, increase in appetite, etc.; 3, reduction in the sedimentation rate and non-flament cell count.

TABLE 2.—RESULTS FOLLOWING INTRAVENOUS SULPHUR THERAPY ARRANGED ACCORDING TO CYSTIN CONTENT OF THE FINGER NAILS.

Cystin content in mg. per 100 mg. of nails.	Types.	No. of cases studied.	Improved.	
			Number.	Per cent.
6 to 7.9	Rheum.	0	0	
	Mixed	2	1	50
	Osteo	2	2	100
	Total	4	3	75
8 to 8.9	Rheum.	3	2	66.6
	Mixed	2	2	100
	Osteo	2	1	50
	Total	7	5	71.4
9 to 9.9	Rheum.	4	3	75
	Mixed	4	2	50
	Osteo	3	3	100
	Total	11	8	72.7
10 to 10.9	Rheum.	8	5	62.5
	Mixed	11	6	55.5
	Osteo	7	5	71.4
	Total	26	16	61.5
11 to 11.9	Rheum.	5	2	40
	Mixed	9	5	55.5
	Osteo	5	1	20
	Total	19	8	42.1
11.9 and above	Rheum.	13	3	23.1
	Mixed	13	4	30.7
	Osteo	7	1	14.3
	Total	33	8	24.2
Grand total		100	48	48

Sixty-seven patients had a cystin content below 12% (Table 2) and 40, (59.7%) were improved; 20 of these had rheumatoid arthritis of which 12 (60%) were improved; 28 patients had mixed arthritis and 16 (57.1%) were improved; while 19 patients had osteoarthritis and 12 (63.2%) were improved. When the cystin content was below normal, the percentage of improvement was essentially similar in all groups.

Of 33 patients with a normal cystin content 8 (24.2%) were improved compared with 40 (59.7%) of the cases with a cystin content below normal.

The Effect of Sulphur Therapy Upon the Sedimentation Rate and Non-filament Cell Count. It was previously shown¹² that the sedimentation rate and non-filament cell count usually are reduced only when there is clinical improvement. The mean sedimentation rate and the mean non-filament cell count were low in this series of patients because most of them had mixed arthritis or osteoarthritis. When the 100 cases are taken as a whole, there is very little change and the mean trend is only slightly affected. In the 48 cases showing improvement, however, there was a reduction of sedimentation rate and non-filament cell count. The mean sedimentation rate was 20.28 mm. before and 14.25 mm. after sulphur medication, a mean reduction of 6.03 mm. The mean non-filament cell count was 15% before and 11.9% after sulphur medication, a mean reduction of 3.1%.

Thus we have a difference of 3.1% between the initial and final mean nuclear counts and a difference of 6.03 mm. between the initial and final mean sedimentation rates. In order to determine that this difference is significant and not due to chance, it is necessary to calculate: 1, the mean; 2, the mean deviation; 3, the standard deviation; 4, the probable error of the mean; and 5, the probable error of the difference.

For these calculations, we have used the standard formulæ as published by Kent.¹³

Standard Deviations: x = initial determinations; y = final determinations. Standard deviation is the constant which has been adopted by biometricians to measure in absolute terms the degree of scatter or dispersion of the variates,

or: $s = \sqrt{\frac{S(X)^2}{N}}$ where s = standard deviation, S = sum and X^2 = the squares of the individual deviations from the mean, and N = the number of values in the series, or: $s = \sqrt{\frac{\text{sum of the squares of the individual deviations from the mean}}{\text{number of cases}}}$

Substituting the value of the nuclear count, $s_x = \sqrt{\frac{1204.96}{48}} = \sqrt{25.10} =$

± 5.01 , or the standard deviation of the initial count. $s_y = \sqrt{\frac{594.06}{48}} =$

$\sqrt{12.38} = \pm 3.52$, or the standard deviation of the final count.

Probable Error of the Mean. $PE_m = 0.6745 \times \frac{s}{\sqrt{N}}$, where PE_m = probable error of the mean, s = standard deviation and N = number of values or cases in the series. Substituting the value of the nuclear count, $PE_{mx} = 0.6745 \times \frac{5.01}{\sqrt{48}} = \pm 0.4876$ or the probable error of the mean of the initial

nuclear count. $PE_{my} = 0.67449 \times \frac{3.52}{\sqrt{48}} = \pm 0.432$ or the probable error of the mean of the final nuclear count.

Probable Error of the Difference. Pearl¹⁴ states that "the probable error of the difference between any two independent quantities (*i. e.*, quantities such that there is no correlation between their errors) is equal to the square root of the sum of the squares of the probable errors of the quantities entering into the difference," or, *i. e.*, $\sqrt{(PE_mX)^2 + (PE_mY)^2}$ = the probable error of the difference, where PE_m equals the probable error of the mean and X and Y the

independent quantities entering into the difference. In this instance, X equals the initial and Y the final nuclear counts.

Substituting the values of the nuclear count, $\sqrt{(0.4876)^2 + (0.3422)^2} = \pm 0.595$, or the probable error of the difference. According to Pearl¹⁴, "It has been practically a universal custom among biometric workers to say that a difference (or a constant) which is smaller than twice its probable error is probably not significant, whereas a difference (or a constant) which is three or more times its probable error is either 'certainly,' or at least 'almost certainly,' significant." The difference equals the initial mean nuclear count minus the final mean nuclear count, or $15.02 - 11.91 = 3.11$. Therefore, $\frac{3.11}{0.595} = 5.226$, or the difference is over 5 times the probable error of the difference.

Using the same formulae, the difference between the initial and final mean sedimentation rates is 3.345 times the probable error of the difference.

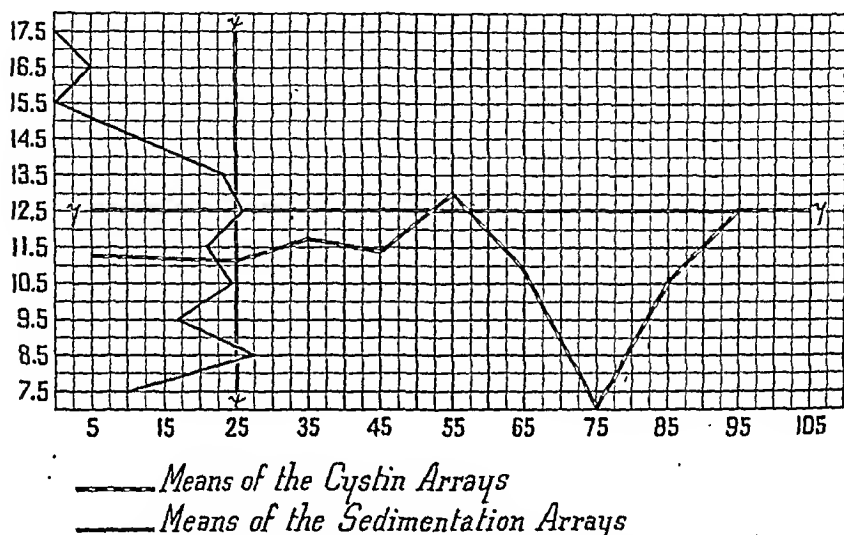


CHART 1.—Observed regression lines showing conclusively the lack of correlation between the cystin content and the sedimentation rate.

We may, therefore, draw the conclusion that the reduction of the sedimentation rate and nuclear count was most certainly significant and not due to chance.

The Correlation Between the Sedimentation Rate and the Cystin Content of the Finger Nails. In a recent article, Argy¹⁵ states that "at least on an average, an inverse ratio between cystin content of the finger nails and sedimentation reaction of the blood does exist in arthritis. This is not true, however, in every instance when individual cases are considered." Only 23 cases were reported, a series too small to be conclusive. We have compared the sedimentation rate and cystin content in 200 cases and have estimated the coefficient of correlation, according to the formulae of Pearl,¹⁴ in 142 cases. In perfect correlation the coefficient is 1 and the nearer the coefficient approaches 1, the better the correlation.

The coefficient of correlation of our series is 0.0196 which is very poor or almost no correlation. It may be concluded, therefore, that

the sedimentation rate and cystin content are in independent series and are not correlated. Their observed regression lines (Chart I) are practically perpendicular, whereas in correlation they are more or less parallel. This further proves that there is no correlation and that their movements are entirely independent; that is, any movement in the sedimentation rate does not affect the cystin content, and *vice versa*.

When an increase in one series occurs in conjunction with an increase in another series, the correlation is said to be positive and the coefficient of correlation is positive. When an increase in one series occurs in conjunction with a decrease in another series, that is, an inverse ratio, the correlation is said to be negative and the coefficient of correlation is negative. In our series, the coefficient of correlation was: (1) small, indicating that there was no correlation; and (2) positive, indicating that no inverse ratio existed.

The Effect of Sulphur Therapy Upon the White and Red Blood Cell Count. There was only a slight variation in the white blood cell counts in this series. The initial mean count was 7450 and the final mean count was 8180. This variation was not considered significant. The red blood cell counts also showed only minor variations. The initial mean count was 4,370,000 and the final mean count was 4,450,000.

Discussion. The results of the present study, as well as the work of others, indicate that colloidal sulphur produces favorable clinical results in a significant percentage of patients with chronic arthritis. The exact mechanism by which improvement occurs is unknown, but enough information is available to enable one to speculate on its possible mode of action. Cawadias¹⁶ states that sulphur plays a very important part in the process of nutrition, particularly the nutrition of joints. Loeper and his associates¹⁷ have noted that the neutral sulphur of the joint cartilage in rheumatoid arthritis was reduced about one-third below normal while the total sulphur of the blood was increased. They also noted that the amount of glutathione in the blood was below normal in a few cases. Cawadias¹⁸ and Race³ found an increase in the urinary output of unoxidized sulphur and the latter believed that there was a deficient oxidation of sulphur in these cases. Schlesinger¹⁹ concurred in the opinion of Hopkins²⁰ that glutathione exists in all cells and that it plays a very important rôle in all processes of oxidation and reduction while others believed that it aids in detoxication. The theory of deficient oxidation of the tissues of the arthritic has long been advocated by Pemberton,²¹ who stated that as a result of impaired circulation in the joints there is poor oxidation and nutrition. This also concurs with the "suboxidative state" mentioned by Llewellyn.²²

Sullivan²³ suggested that inasmuch as glutathione aids in detoxication, its deficiency, as a result of improper metabolism, might allow uncontrolled action of the noxious agent in the arthritic. He be-

lieved that the administration of sulphur in these cases prevented the normal body sulphur complexes from being diverted into other channels. A low blood glutathione and a low cystin content of the finger nails, therefore, might indicate that there is a deficient oxidation of sulphur in these cases and, as it apparently plays a part in oxidation and in the nutrition of the joints, this may be the underlying factor in sulphur therapy.

The low cystin content in 67% of the cases studied compares closely with the 65% of Sullivan and Hess⁷ and the 75% of Neligan¹⁰. When there was a subnormal cystin content, it was usually increased with sulphur therapy both when it was given by the intravenous and the intramuscular methods.

Except in a few cases, there was a reduction of the sedimentation rate and non-filament cell count with sulphur medication but there was only a slight reduction following placebo medication. The cases showing improvement with colloidal sulphur therapy are, as a rule, those in which vaccine therapy is of the least benefit. In young people with rheumatoid arthritis, for example, the cystin content is usually normal and sulphur is of little benefit, whereas in older people with rheumatoid arthritis and in patients with mixed arthritis and osteoarthritis, the cystin content is frequently low and sulphur therapy is often beneficial.

Those patients who showed improvement in the focal symptoms also showed marked improvement in constitutional symptoms, *i. e.*, less fatigue, an improved appetite and gain in weight. They were less depressed and assumed a more cheerful attitude toward the disease.

Although our results have not been as encouraging as those reported by some authors, we believe that sulphur is a valuable agent in the treatment of arthritis.

Conclusions. 1. Fairly large doses (10 to 30 mg. twice weekly) of colloidal sulphur, as a rule, are well tolerated.

2. With the larger doses, however, some patients developed symptoms of toxicity, such as fatigue, drowsiness, headache, increased pain, stiffness or swelling of joints but they usually disappeared in 5 days and were never severe enough to cause anxiety.

3. When the cystin content of the finger nails was below normal, it was usually increased with sulphur therapy.

4. The percentage and degree of clinical improvement was greater in those patients with a subnormal cystin content than in those with a normal content.

5. The percentage and degree of clinical improvement was greater with sulphur than with placebo therapy.

6. Sedimentation rates and non-filament cell counts were reduced in those cases showing clinical improvement.

7. There was no significant effect upon the red and white blood cell counts.

8. We believe that colloidal sulphur is a valuable agent in the treatment of certain types of arthritis.

We wish to express our thanks to Miss M. Jordan and Miss J. Weitzman for their assistance in this study.

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THE BACTERIAL FLORA ASSOCIATED WITH FOREIGN BODIES IN THE TRACHEA AND BRONCHI.*

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WHEN a foreign body lodges in the air passage ways there is an inflammatory response on the part of the tissues more or less severe.

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Jackson¹ and McCrae² have studied this response clinically. According to them it depends upon the type of the foreign body, its length of sojourn in the tracheobronchial tree, the amount of occlusion occasioned by it, the age of the patient, and subsequent infection. Their studies do not include the bacteriologic findings in these cases. This paper deals with the bacteriologic data incident to a foreign body in the respiratory tract.

With the exception of my preliminary report³ on the bacterial flora and tracheobronchial foreign bodies there is no systematic study on the subject. A few references to isolated cases have been listed in the American and German literatures.

The Material. The material for this study has been furnished by the Bronchoscopic Department of this hospital, the services of Dr. Chevalier Jackson and his successor Dr. Louis H. Clerf. There were 243 patients with tracheobronchial foreign bodies. Cultures of samples of mucus obtained bronchoscopically from the site of the foreign body in the air passageways form the basis of this report.

The method of collection of the mucus from the respiratory tract is important. Having introduced a laryngoscope, the surgeon passed a bronchoscope through its lumen thereby avoiding contamination of the latter with oral secretions. The mucus was collected on small sterile gauze swabs or by means of an aspirator passed through the bronchoscope. The latter method is preferable; the former a necessity when the secretion is scanty. The foreign body itself has never been cultured since in its removal it is usually contaminated with the secretion of the buccal cavity.

I believe that the microbic content of pus so collected is more representative of the bacterial flora in the lesion than that of expectorated material. The evidence for that statement is based upon the following data. Pure cultures of bacteria have very occasionally been obtained from pus so collected. Secretions aspirated from individuals with a normal tracheobronchial tree, upon whom diagnostic bronchoscopies were performed, have contained few organisms; occasionally none were recovered. It can be demonstrated by growths obtained from pus repeatedly recovered from the same pulmonary abscess or bronchiectatic cavity that there is a variation in the bacterial population depending on the season of the year. Cultures seeded simultaneously from the tracheobronchial and oral secretions, equal amounts of each sample having been used, yielded organisms more or less similar in kind but quantitatively different. This is reasonable since the secretion from the lower respiratory tract contaminates the oral cavity when it is expectorated. Though contested by some, nevertheless there is abundant evidence to support the view that bacteria are constantly getting to the lower respiratory levels from above. How long they live and how well they thrive there, is another problem.

As an additional test, Dr. Clerf had a metal collar fitted on the pus collector. It was so constructed that it fitted the bronchoscope snugly and prevented the collector from coming in contact with the lateral walls of the bronchoscope. A sufficient number of mucopurulent specimens were collected from the trachea and bronchi with and without the collar to justify the conclusion that this source of contamination is negligible.

Technique. Smears were made and stained by Gram's (Burke's modification) method. Acid-fast and other stains were employed when indicated. Most of the specimens were also studied by dark-field examination to determine the presence or absence of spirochetes. Samples of pus were directly seeded on beef infusion agar plates containing about 5% of human blood

and in 1% dextrose bouillon, dextrose hormone broth since 1927. All media had a pH value between pH 7.5 and pH 7.8. The cultures were studied and transfers were made at the end of 48 or 72 hours. The plates were kept for a longer period before being discarded. The usual standard bacteriologic methods were used to classify and identify the organisms.

Essential differences and additions to the technique outlined above were employed as here indicated. A portion of a large number of specimens containing pneumococci was injected into mice and the pneumococcus typed. When there was any reason to suspect tuberculosis, guinea pigs were inoculated and the material seeded on Corper's or Loewenstein's mediums. A number of anaërobic cultures were made. I employed several methods; an anaërobic jar combining air exhaustion, nitrogen replacement and removal of the residual air with pyrogallic acid and sodium hydroxid, Zinsser's and Spray's anaërobic plate methods, Liborius' method plus an oil seal and Buchner's and Tarozzi's methods.

To have a basis of comparison for the bacterial findings a brief résumé of some of the clinical factors is necessary. Foremost is the foreign body itself. Jackson¹ and later McCrae² have directed attention to the differences in the local and general reaction of the patient with different kinds of foreign bodies. They observed in general, that foreign bodies consisting of animal and plant substance occasioned marked reactions and that certain ones, such as the peanut, were very prone to be associated with grave clinical features. With this in mind I have divided the foreign bodies as follows: 76 inert objects, pins, safety pins, needles, tacks, buttons, nails, screws, toys, dental fixtures and instruments, wire, beads, pencil caps, bullets, celluloid, pebbles, glass, bird shot, and a primer cap; a second group consisting of 8 bones and 22 teeth; and a third group consisting of 73 peanuts, and a final group chiefly vegetal substances consisting of 21 nuts and nutshells other than peanuts, 5 heads of timothy grass, 7 corn grains, 10 beans (navy, coffee and lima), 9 watermelon seeds and 15 miscellaneous, including peas, wood, pills, meat, apple, carrot, prune, potato and fruit seeds.

Age exerts a profound influence on the course of the disease. In this group the ages ranged from 8 months to 67 years. The youngest, a very ill child, aspirated the head of a blade of timothy grass. It was located in the right main bronchus and was removed after 7 days' sojourn. From the pus, *Strep. hemolyticus*, *S. aureus*, *B. influenzae*, *Diplococcus pneumoniae* and *Micrococcus catarrhalis* were isolated. The oldest patient had a dental fixture in his left bronchus for 3 weeks and a day. There was a profuse growth of *S. aureus* with a few colonies of *Diplococcus pneumoniae* on the plates. The distribution of foreign bodies relative to age is significant. In the inert group there are 3 peaks, the first between the second and third years, the second between the fifth and sixth years, and the third in the second decade. The greatest number of peanuts and other vegetal foreign bodies are aspirated between the first and second years of life while the maximum for the aspiration of teeth and bones is reached in the fourth decade.

An analysis of the lengths of sojourn of the foreign bodies in the respiratory tracts indicate that the largest number, 44, were retained from 1 to 2 weeks; a second group of 20 for 3 days, and a third of 9 for 1 to 2 years. One, a nail in the bronchus of the right lower lobe of a woman aged 24, was in the bronchus for 18 years. The pus contained *Strep. hemolyticus*, *S. albus* and *Micrococcus catarrhalis* and the comment on my record is "She is not very ill."

In 144 cases of which I have a record, 18 of the foreign bodies were in the trachea, a part of one was located in both main bronchi, 72 in the right main or stem bronchus, 33 in the right lower bronchus, 5 in the left upper bronchus, 47 in the left main bronchus, 11 in the left lower bronchus, 5 in the right upper bronchus, 1 in the lung and 1 in the (right) middle lobe bronchus. The amount of obstruction is difficult to tabulate. In some instances the obstruction was complete while in other cases there was good drainage in spite of the presence of the foreign body. There were all grades and degrees of obstruction. The authors cited above have directed attention to the foreign body that frequently acts as a ball valve.

TABLE 1.—BACTERIA ISOLATED WITH VARIOUS TYPES OF FOREIGN BODY.

Bacteria.	Times isolated.	Foreign bodies and percentages of isolations in:			
		76 inorganic.	22 teeth 8 bones	73 peanuts.	67 vegetal.
<i>Streptococcus hemolyticus</i>	63	22	26	26	20
<i>Streptococcus viridans</i>	85	25	43	31.5	44.7
<i>Streptococcus non-hemolyticus</i>	29	14.4	10	8.2	13
<i>Diplococcus pneumoniae</i>	94	32.8	46.6	43.8	32.8
<i>Neisseria</i>	153	55	56.6	73.9	59.5
(<i>N. catarrhalis</i> , <i>N. sicca</i> , <i>N. flava</i> , <i>N. subflava</i> , <i>N. crassa</i> , <i>N. mucosus</i>)					
<i>Corynebacteria</i>	54	21	13	26	22
<i>Staphylococcus pyogenes aureus</i>	54	38	26.6	23.2	16
<i>Staphylococcus pyogenes albus</i>	65	33	43	42	31
<i>Mycobacterium tuberculosis</i>	1	1	0	0	0
<i>Bacillus mucosus capsulatus</i>	18	9.2	0	5	10
<i>Hemophilus influenzae</i>	34	5.2	33	16	11.9
<i>Bacillus coli communis</i>	2	1	0	0	1.4
<i>Bacillus coli communior</i>	2	1	0	0	1.4
<i>Micrococcus tetragenus</i>	11	6.5	6.6	2.6	2.9
<i>Bacillus bronchisepticus</i>	1	1	0	0	0
<i>Bacillus subtilis</i>	1	1	0	0	0
<i>Proteus vulgaris</i>	1	...	1.3	0	0
<i>Vibrio</i> (unidentified)	2	2.6	0	0	0
<i>Monilia</i> (Castellani)	6	2.6	0	1.3	4.4
<i>Bacillus fusiformis</i>	2	2.6	0	0	0
<i>Spirochaeta</i>	2	2.6	0	0	0
<i>Actinomycetes</i>	2	0	0	2.6	0

Results. Table 1 is a summary of the number of times each bacterium was isolated and the percentage of times it was isolated in each group of foreign bodies. I have classified the *Neisseria* as a group; they can hardly be regarded as very potent pathogens. For the same reason the *Corynebacteria* are put in a group. *Corynebacterium diphtheriae* was never isolated. A certain ill-defined group of organisms, thread-like in structure, branching or non-branching, and referred to under many names, I have grouped as *Actinomycetes*. By *Monilia* I mean certain yeast-like organisms classified by Castellani: *Mycobacterium tuberculosis* was recovered

once from the bronchus of a tailor, aged 67, who aspirated a tooth a month prior to the time of taking of the culture. He had had tuberculosis for many years. In addition to the tubercle bacillus, *S. aureus* and *Diplococcus pneumonia* were recovered. Table 2 is a comparison between the more important bacteria and age groups. There is a sufficient number of cases from the first to the eighth years and in the first decade to provide some idea of the frequency of organisms at these ages. For the other ages the number of cases is too few for conclusions to be drawn. Cultures have practically always contained more than one kind of organisms. Pure cultures from this source are the exception rather than the rule. Sometimes as many as 7 or 8 kinds of bacteria have been recovered. I have purposely not listed anaërobic bacteria because the total number of cultures so made is not sufficient for comparisons. One point is reasonably certain, however, many of the cultures did not develop a growth under anaërobic conditions. The anaërobic organisms most frequently recovered were streptococci. They can be put down as anaërobic and partially anaërobic organisms. At one time in this study a rather large series of pneumococci were typed; by far the greatest number of these were of Type 4.

TABLE 2.—RELATION OF BACTERIA ISOLATED TO AGE GROUPS.

Age of patient Number of pa- tients	Years.															
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-20	20-30	30-40	40-50	50-60	60-70
	4	31	41	23	17	17	15	8	7	10	14	10	11	5	4	4
	Occurrence in percent age.															
<i>Streptococcus</i> hemolyticus	75	22	34	34	29	13	26	25	14	40	32	20	18	45	50	0
<i>Streptococcus</i> viridans		48	29	43	64	29	66	25	14	50	50	80	35	20	50	0
<i>Streptococcus</i> nonhemolyticus		19	12	17	5	17	6	37	14	20	5	20	9	0	0	0
<i>Staphylococcus</i> albus	75	60	39	41	29	29	33	37	14	20	38	40	11	20	0	0
<i>Staphylococcus</i> aureus		35	19	17	41	17	26	87	28	20	33	30	0	60	50	25
<i>Pneumococcus</i>		60	22	5	35	11	40	25	25	0	33	40	35	40	25	0
<i>B. influenzae</i>		9	12	12	17	47	5	20	12	14	20	33	20	0	60	0
<i>B. mucosus</i> capsulatus		19	9	4	17	0	6	0	14	10	5	10	9	0	25	25

Comments. Comparing the microorganisms recovered with the foreign bodies it is apparent there is little difference in the frequency of occurrence of organisms in the different series of foreign bodies. The figures for hemolytic streptococci have percentages which approach each other numerically. In the group of peanuts there were 43% of pneumococci against 32.8% in the other vegetable foreign bodies, and 46.8% among the teeth and bones. Since peanuts and other vegetable substances are of a similar nature and

teeth and bones dissimilar, the close numerical ratio between unlike foreign bodies and its disproportion in like ones makes it evident that the foreign body of itself does not influence the character of the bacterial flora. Similar differences may be observed for the other organisms such as the staphylococci, *Strep. viridans* and *H. influenzae*. In brief the organisms and the foreign body bear no direct relation to one another.

In the comparison between bacteria and age groups the situation is similar. In those instances in which the groups are large enough the same kind of disproportion between age groups and bacteria is apparent. The same sort of thing is so obvious with regard to length of sojourn of the foreign body in the respiratory tract and its location there, that I have not deemed it necessary to exhibit tables.

One might ask if this study of the flora in these cases demonstrate anything worth while. I believe it does. Since the bacteria recovered from the lesions are similar to the organisms of the mouth it is reasonable to suppose that some of them were aspirated with the foreign body or that they were present at the site of the lesion when the foreign body was aspirated. This is even more apparent when one considers the presence of *M. tuberculosis* in an instance in which there can be no argument, since the patient was known to have suffered from tuberculosis for many years. The occurrence of organisms, rather unusual for the respiratory tract, like *Prot. vulgaris* and *B. coli* is fairly good proof of contamination of the foreign body with these organisms. Most of the microorganisms recovered, are capable of setting up pyogenic infections. Since the pus usually contained several kinds of bacteria, it is not possible to be absolutely certain which is the exact exciting agent. Yet there are certain characteristics of growth about some of these organisms that seems significant. Chief among them is the quantitative difference of growth of the bacteria on a single blood plate. Very often it happens that upon such plates almost all of the bacterial colonies are of one kind. There are colonies of other bacteria present but they are few in comparison. This phenomenon is particularly striking with reference to *S. aureus*. From my observations of bacteria isolated from several thousand pulmonary lesions other than those resulting from foreign bodies I have observed how often *S. aureus* exhibits this property in this instance and how rarely one sees plates seeded from the pus of a pulmonary abscess, or a bronchiectatic cavity like them. The latter lesions, however, are far more common. When such an incident occurs it is fairly good presumptive evidence that the organism is the likely etiologic factor.

With regard to the degree of severity of the lesion, one is not often able to restrict its cause to one or the other type of organism present. All of the evidence seems to point to the conclusion that other things being equal one kind of bacterium is as capable as another of producing severe reactions. One of the most noteworthy

features in this respect is the frequent occurrence of the pneumococcus in these lesions. Yet Dr. Thomas McCrae, remarking that he had not observed pneumonia in any of these cases, suggested that there is food for thought on the pathogenesis of pneumonia in this connection.

While the importance of the bacteria is not to be minimized in the reaction occasioned by this accident, the type of foreign body and obstruction to drainage are the more important etiologic factors. The lesions have many things in common with obstructive lesions elsewhere in the body such as an obstructed sinus, gall bladder, or ureter. Sooner or later infection follows in their wake. In the tracheobronchial tree this usually occurs earlier than in some of the other localities of the body and it is often more apparent because of the extreme youth of the patient and the danger to life.

Summary. 1. Cultures seeded from pus bronchoscopically collected from the trachea and bronchi furnish more reliable data on the kind of microorganisms there, than those seeded from expectorated material.

2. The bacterial flora present in the air passages in which a foreign body is lodged does not materially change with the type of foreign body, its location or length of sojourn there, the age of the patient and degree of obstruction induced by it.

3. Other things being equal, one pathogen seems as capable as another of producing severe grades of infection in an obstructed tracheobronchial tree.

4. Quantitative differences in the numbers of colonies of different organisms on a plate of blood agar seeded from pus recovered from these lesions are a reliable guide in estimating the part that a given organism plays in the resulting infection.

5. The indications from a limited number of studies of the anaërobic bacteria from such lesions are that they are of minor importance.

6. The bacterial invasion and infection of the tissues of the lower respiratory tract at the site of a foreign body seem to follow the same general principles as those encountered in obstructive lesions elsewhere in the body. The irritation produced by the obstructing body itself and the amount of hindrance to drainage, primarily, and, secondarily, other factors favoring or hindering microbic multiplication such as the age and hardihood of the tissues, pressure on them and the duration of the irritation, determine and limit the infection.

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THE DIFFERENTIAL BLOOD PICTURE OF A GROUP OF RURAL INHABITANTS OF ALABAMA.*

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THE functions of the eosinophils, the basophils and, to a lesser degree, the lymphocytes and monocytes, are not as well understood as are those of the neutrophils. Any observations which tend toward the explanation of their function or an analysis of factors associated with relative or absolute changes in the percentage of these elements in the blood should be of value. It is primarily for such a reason that this paper is written.

It analyzes the laboratory findings in 706 of the 849 persons studied during a public health survey in Bullock County, Ala., during 1934. In 143 no laboratory test or specimens were obtained for examination, for one reason or another. This survey was a house-to-house study to determine the prevalence of syphilis, positive tuberculin tests, malaria and intestinal parasites (chiefly hookworms) among the colored people living in and around Union Springs, Ala. Special care in the survey was given to environmental and related factors. When more cases are worked up, an attempt will be made to analyze the influence of these socio-economic factors. In this report, divided into five groups, however, we shall give only the laboratory findings.

There were 462 persons in the first group; 401 of them were between the age of 5 and 34 years. The differential white cell counts are given of these 401 persons who were our "normals" in that they did not have either a positive malarial smear, animal parasites in the stool examination, a positive tuberculin, or history of any of the diseases generally associated with an increase of eosinophils. In the second are the results of 47 persons with positive stool examination for intestinal parasites, chiefly hookworms or ascarids. In the third are the results of 71 persons whose blood smears showed malarial parasites. In the fourth are the results of 60 persons in whom the tuberculin tests were positive. In the fifth are the results of 153 persons who gave some history or showed some symptom that might be regarded as related to an existing increase in eosinophils. Among the conditions considered in this last group are asthma, hay fever, various types of skin lesions, history of food sensitivity or of previous serum inoculations.

* This study was made under the direction and advice of the Rockefeller Foundation.

GROUP I. "NORMALS." All of the persons of Group I were objectively and subjectively healthy. A complete white cell differential examination of one or more blood smears from each of them was done. Between 100 and 250 white blood cells were examined from each person. The percentage of the eosinophils and of the number of granules in these eosinophils appeared to be higher than that usually accepted as normal in most laboratory manuals. These results were arranged into seven classes according to age and are given in Table 1.

Because of the small number of infants or very young children examined and the highly labile erythrocytic and leukocytic blood picture in young children, as pointed out by Goldhamer,¹ in 1932, Klenerman² and others, in 1934, their results are not recorded in the table. The eosinophil and monocyte percentages were higher than for the class from 5 to 9 years.

TABLE 1.—THE AVERAGE PERCENTAGE DIFFERENTIAL OF WHITE BLOOD CELLS IN A GROUP OF APPARENTLY HEALTHY INDIVIDUALS LIVING IN ALABAMA.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes.		Monocytes, %	Number examined.
				Small, %	Large, %		
5-9 . . .	51.0	12.7	1.7	15.1	11.2	8.0	110
10-14 . . .	54.0	9.0	0.9	16.0	12.0	8.1	97
15-19 . . .	54.3	10.3	0.5	13.1	11.0	10.3	67
20-24 . . .	55.7	8.1	0.8	10.0	18.3	7.9	41
25-29 . . .	64.0	7.0	1.0	12.0	10.8	6.0	50
30-34 . . .	61.3	5.9	0.0	18.3	9.0	7.0	36

Even when our adults were compared with the differential graph of Needles³ (1932), there are cellular differences, of which only the eosinophil differences are statistically significant. Needles's results, obtained from 100 nurses, and our results from 158 individuals between the ages of 15 and 30 years, are as follows:

	Neutrophils, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %
Needles' figures . . .	70.0	24.6	3.2	1.7	0.5
Our figures	57.3	24.3	8.3	8.6	0.7

All of our smears were stained with either Wright's stain for blood films or Giemsa's blood stain. In our group the 24% lymphocytes were 11% small lymphocytes and 13% large lymphocytes.

The average number of granules in the eosinophils is given in Table 2. The total number of granules is counted in 2 eosinophils from at least one of the slides from each person recorded. These two eosinophils from each slide that were counted constitute as nearly a random sample of normal eosinophils as was possible. The objective of the microscope was focused on different parts of different slides, and the granules in the first 2 eosinophils that came into the field of the objective were counted. By varying this with each slide, we were able to avoid the effects of margination fre-

quently seen in the more sticky leukocytes in blood smears. Eosinophilic myelocytes were excluded from this table, so the results in Table 2 are of normal eosinophils with 2 or more lobes in their nuclei.

Realizing that many of these persons ate pork which was not government inspected and which might result in a mild trichinosis, special efforts were made to exclude such cases from this group by history. No biopsies were done.

TABLE 2.—THE AVERAGE NUMBER OF GRANULES IN EOSINOPHILS IN DIFFERENT AGE CLASSES.

Age group, yrs.	5 to 9.	10 to 14.	15 to 19.	20 to 24.	25 to 29.	30 to 35.
Eosinophil granules .	140 \pm 6.2	109 \pm 6.6	110 \pm 6.6	114 \pm 5.2	94 \pm 5	101 \pm 6.4
Persons examined .	16	11	10	10	17	6

Considering the reports of Biggart⁴ (1932) and of Stephens⁵ (1935) of the probable proliferation of some of the eosinophils from sources other than the bone marrow, palpation was done to determine the prevalence of superficial lymph adenopathy and enlarged spleens. There was found in this group a higher incidence of non-tender palpable lymph nodes, but the splenic index was less than in Group III, where the blood was positive for malaria and where the eosinophils were lower.

From the graphs of Custer and Ahlfeldt⁶ (1932), a composite graph may be made which shows the variation in the cellularity of the bones of the tibia, femur, ribs, sternum and vertebra with changing age. When a composite graph showing the red (blood-forming) marrow is compared with the eosinophil changes with age, the correlation is very high up to the age of 15 years. We feel that some additional knowledge may be obtained by a more careful study of the cellularity of bones in animals in which a high eosinophilia may be produced, along with anaphylactic studies in animals. Any definite displacement of yellow (fatty) marrow by red (blood-forming) marrow, if carefully controlled and correlated with the changes in the cellular elements of the blood under acute experimental controlled conditions, would appear of value. We are outlining a protocol for such an experiment with the aid of the Department of Pathology.

The purpose of eosinophil increase is apparently defensive, acting not against bacterial diseases, but chiefly toward detoxifying, destroying and removing incomplete protein metabolic products which are injurious to the body. Hadwen⁷ (1925) also thinks that the eosinophils may secrete substances which are injurious to the worms themselves in helminth infestation.

Since Klinkert⁸ (1911), Armand-DeLille, Hurst and Sorapure⁹ (1930), and Stewart¹⁰ (1933), there have been reported cases of "familial" or "constitutional" eosinophilia in which persistent and unexplained eosinophilia of a high degree occurred in certain families. We attempted to analyze our cases to see if the high average percentage was peculiar to certain families. It did not appear sufficiently definite as a family trait to explain the high average eosinophilia.

With the demonstration of the clinical significance of the different nuclear forms of the neutrophils by Arneth¹¹ (1904), and the correlation of these changes with hematopoietic activity by Schilling¹² (1920), several investigators have recorded observations and discussed their significance (Cooke and Ponder¹³ [1927], Farley and others¹⁴ [1930], Kohlman¹⁵ [1931], Mullin and Large¹⁶ [1931], Fitz-Hugh¹⁷ [1932], Gorsky¹⁸ [1932], and Needles³ [1932]). Most of their discussion centers around the diagnostic and prognostic value of a more efficient interpretation of the changes in the percentage of cells of the neutrophilic series when divided according to the age of the cell or their nuclear configurations. The importance of repeated counts on the same individual is emphasized, in order to determine not only the percentage at any one time, but the various types of shifts.

We present, for comparison with Needles³ (1932) in normal nurses in Michigan, a hemogram of 100 similar count on 158 apparently healthy negro adults in rural Alabama between the ages of 15 and 29. In my group, the males and females are about equal.

Class.	I.	II.	III.	IV.	V.
Normal nurses (Needles)	8.4	22.9	26.7	8.7	3.2
Our normal negroes	11.0	17.6	18.9	7.6	1.9

The neutrophils were 57.3% of the white cell count in our series. In this hemogram, Class I represents the non-filaments, while Class V represents those of 5 nuclear lobules connected by filaments.

GROUP II. PERSONS HARBORING INTESTINAL PARASITES. Under the heading of monocytes are placed both the large mononuclears and the transitionals because they respond to the same stimuli, probably coming from the reticuloendothelial system, according to Gorsky¹⁸ (1932). According to Poindexter¹⁹ (1934), the platelet response is associated with the same stimuli. In 1 boy, aged 8 years, who was highly infested with hookworms, as determined by the Stoll count, there was found not only 31% of eosinophil leukocytes, but also 4% of eosinophilic myelocytes with their rounded, non-lobed nuclei. While we did not rule out a malignant tumor or leukemia, we could not find any further evidence to suggest either of them.

TABLE 3.—THE AVERAGE DIFFERENTIAL WHITE CELL COUNT ACCORDING TO AGE IN 47 PERSONS WITH INTESTINAL PARASITES.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes.		Monocytes, %	Number examined.
				Small, %	Large, %		
5-14 . . .	48.1	21.7	0.6	12	9	9.0	26
15-24 . . .	53.0	14.9	0.9	12	12	6.1	14
25-35 . . .	62.6	12.5	0.6	11	9	3.1	7

GROUP III. PERSONS INFESTED WITH MALARIAL PARASITES. Table 4 gives the results of persons who gave a positive blood smear for malarial parasites. While some of these patients were very anemic and gave a history of chills and fever at various times within the last year, none of them was confined to bed or acutely ill at the time the blood smears were taken.

TABLE 4.—THE AVERAGE DIFFERENTIAL WHITE CELL COUNT ON A GROUP OF 71 INDIVIDUALS FROM WHOM A BLOOD SMEAR WAS POSITIVE FOR MALARIAL PARASITES.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes.		Monocytes, %	Number examined.
				Small, %	Large, %		
5-14 . . .	53.9	6.4	1.0	13	15	10.0	37
15-24 . . .	57.0	6.0	1.3	12	12	10.6	22
25-35 . . .	62.1	4.9	1.3	13	11	6.8	12

The two chief observations here are the lower eosinophil and the higher monocyte percentage. The latter is what would be expected, but the former is still controversial. Some observers contend that there is an eosinophilia in chronic malaria, while others say that there is a decreased eosinophil percentage with the increase in anemia from the malaria. In this group, which is composed primarily of carriers, we did not find a high eosinophil percentage. The differential blood picture did not correlate highly with that of patients inoculated with the malarial parasite for the treatment of paresis, as reported by Winfield²⁰ (1932).

GROUP IV. PERSONS WITH POSITIVE TUBERCULIN TEST. Table 5 shows the results of a study of the differential count of a group of persons living in rural Alabama who reacted positively to an intracutaneous injection of 0.01 mg. of O.T.

TABLE 5.—AVERAGE DIFFERENTIAL WHITE CELL ON A GROUP OF 60 PERSONS WHO GAVE A POSITIVE TUBERCULIN REACTION.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes.		Monocytes, %	Number examined.
				Small, %	Large, %		
5-14 . . .	56.1	8.5	0.8	16	14	4.5	19
15-24 . . .	61.0	5.9	0.8	15	12	4.1	30
25-35 . . .	62.1	3.8	1.1	15	13	4.1	11

Of the 706 individuals who had various tests and examinations, 576 had the tuberculin test. Sixty (10.4%) gave positive tuberculin.

When these results were divided according to age, 6% of those between the ages of 5 and 14 years gave positive tuberculin; 19% between 15 and 24 years and 21% between 25 and 35 years. The highest incidence was among those who gave a history of working or living in the nearby towns or city during the season when they were not planting or harvesting.

GROUP V. MISCELLANEOUS. The results of this group are listed in Table 6. This group contains a miscellaneous group of 153 individuals who either gave a history of some type of sensitivity or dermatitis. One case in this group was infested with *Cochliomyia macellaria* at the time the smear was taken. None of them was confined to bed at the time the blood for the differential was taken.

TABLE 6.—DIFFERENTIAL BLOOD COUNT IN CASES OF SENSITIVITY OR DERMATITIS.

Age group, yrs.	Neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes.		Monocytes, %	Number examined.
				Small, %	Large, %		
5-14 . .	56.1	9.0	1.1	17	14	2.9	40
15-24 . .	59.6	11.4	1.0	13	11	3.8	64
25-35 . .	64.3	11.6	1.0	11	10	2.6	49

Discussion. While least is known about the function of the basophils, the eosinophils certainly appear to be next. The frequent association of hypereosinophilia with certain clinical conditions and following sensitivities of certain types of parenteral protein administration, has been sufficiently frequent to warrant the hypothesis that it is a response to incomplete protein metabolic products in the body.

Kelly²¹ (1935) reports a 92% eosinophilia in a boy, aged 10 years, with 180,400 white blood cell count. The only positive facts were a pain in the joints, a history of fever and a questionable cardiac murmur and an enlarged spleen. He thinks that certain persons have a highly sensitive blood-forming system and an allergic response to a stimulus, which may express itself in the form of hypereosinophilia instead of by a temperature or skin reaction as seen in certain responses to bacterial or animal proteins or pollens.

A report of eosinophilia in a case of dermatoneuromyositis by Sluzewski²² and others (1931), in which no other explanation was found, and the reference of Stitt²³ (1917) to the belief of Neisser that increased eosinophils may be due to an expression of the sympathetic system irritation, places that system under scrutiny. McCulloch and Dunlap²⁴ (1932), however, did not find the eosinophil percentage markedly disturbed in either hyperthyroidism or hypothyroidism. Cooke²⁵ (1932) thinks that the hereditary (atopic) factor in asthma, while not causal, may be responsible for the creation of an offspring of a more sensitive system, with a tendency toward the capacity for allergic manifestation, and the hematopoietic system, from which the eosinophils come, may be a part of this

inherited sensitive system to allergic or anaphylactic reactions. The system from which the eosinophils come may be either the bone-marrow, hemolymph nodes or their equivalents.

Animal experimental evidence and clinical observation have led Banerji²⁶ (1933) and Chillingworth²⁷ (1934), to believe that the increased eosinophilia in asthma is associated with the overdistention of the alveolar spaces. Associated with this alveolar distention are repeated forceful expiration, increase in carbon dioxid tension and probably disturbance of the acid-base equilibrium which may reflexly stimulate the sympathetics.

The explanation of the differences in percentage of some of the formed elements in the blood of this group of rural negroes living in Alabama, when compared with the average for the country as a whole, or with studies in a northern state, as Michigan, is not known. Whether there are racial, meteorologic, occupational, nutritional or obscure infectious factors which seem to be able to change the pattern of a differential count, are points which further study may clear up. The dietary habits of most of these people were conducive to vitamin deficiencies. While the cases of pellagra occasionally seen were not included in these averages, mild cases in the early stage may have been included unknowingly. This is especially worthy of thought when we realize that the dermatologic manifestations, which generally attract our attention, are secondary to neurologic damage. In this way the effects may be at work for a long time before they are externally manifested. The findings of this group compare favorably with those of a group of natives of Guam who were similarly studied. We hope others who may be interested in these facts may check them by similar studies of small localized groups under somewhat comparable conditions.

Because we did not find any parasites in the stools of the normals, we are not ready to say that the increased eosinophils were not associated with previous helminth infestations, since small numbers of ova in the stool, or a stool temporarily free from ova, are certainly not a criterion of previous infestation and not an absolute criterion of the absence of a small, relatively inactive female infestation, or a male infestation, either of which may cause some eosinophilia. This is probably not the case, however, as the age variation in the eosinophil percentage in the normal group did not correspond to the relative prevalence according to age, of hookworm infestation.

Summary and Conclusion. We have presented the results of our observations on white blood cell differentials from a group of rural negroes living in Bullock County, Ala. In laboratory studies, on 706 of the 849 persons studied, 401 were found to be free from animal parasites and other allergic diseases. These served as "normal" controls. This group, as well as the malarial positive, hookworm positive, tuberculin positive, and those with a positive listing of sensitivity, gave an average white blood cell differential

which does not correlate with that usually recorded in manuals as guides, and averages from more northern climates, and of persons of different occupations. The most consistent differences were a lower neutrophil percentage and a higher eosinophil and monocyte percentage in our group. This was true not only with those having some condition which could explain this difference, but also with the so-called normals. The most pronounced unexplained difference was the high eosinophil average. The average number of granules in the eosinophils was higher in those with the larger percentage of eosinophils. The question of whether these differences are racial, meteorologic, occupational, nutritional, obscure, infectious, or a combination of these or other factors, is not answered.

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(Titles have been omitted for sake of brevity.)

BOOK REVIEWS AND NOTICES

DIET CONTROL. A System of Eleven Hundred Diets for the Prescription of Diabetic, Anti-obesity and Measured Diets in General. By GEORGE E. ANDERSON, M.D., Attending Physician to the Brooklyn and the Lutheran Hospitals; Chief of Metabolic Clinic, the Brooklyn Hospital, and PAUL CHADBOURNE ESCHWEILER, M.D., Assistant Attending Physician to the Brooklyn and the Methodist-Episcopal Hospitals; Senior Physician, Metabolic Clinic, the Methodist-Episcopal Hospital. Unpagged. New York: Gallo & Ackerman, Inc., 1935. Price, \$3.50.

THIS unique offering presented in a loose leaf cover contains a booklet of descriptive text relative to diet prescriptions. It offers a quick, moderately accurate presentation of caloric values and all necessary tables for establishing a dietary for the uncomplicated diabetic arteriosclerotic, diabetic children and the obese. Subsequent material consists in twenty individual diet booklets for the patient with readily understandable instructions and food table data.

The authors consider this a simple flexible method for the prescription of measured diets with ample latitude for modifications as the occasion arises.

The Reviewer feels that the material is aptly suited for workers in metabolic clinics and practitioners' offices where a ready dietary clearly presented is a necessity. The presented food tables lack in accuracy and completeness in relation to the rapid strides shown in the field of nutrition during the recent years, but they present the orthodox routine analyses.

M. B.

THE SPLEEN AND RESISTANCE. By DAVID PERLA, M.D., Associate Pathologist and Bacteriologist, Montefiore Hospital, and JESSIE MARMORSTON, M.D., Associate in Pathology, Cornell University Medical College. With a Foreword by DAVID MARINE, M.D. Pp. 170. Baltimore: The Williams & Wilkins Company, 1935. Price, \$2.00.

THE effect of the spleen on resistance to infectious and metabolic diseases, neoplasms and other disorders has long been a subject that has engaged the attention of medical investigators, both for its scientific interest and practical importance in handling disease. This book presents not only a critical review of the complex literature on the subject but also the authors' not inconsiderable personal contributions. In the important question of the relation of the spleen to bacterial antibodies the authors conservatively conclude that it has a marked ability to fix antibody, and that its importance in antibody production is strongly suggested but not unequivocally established; it "is essential in the maintenance of the natural resistance" to certain infections in many species.

While the evidence is adequately presented and in general the deductions are acceptable, to some statements exceptions must be taken: the light area in the center of the Malpighian follicles definitely is not a "germinal center consisting of dividing lymphoblasts" (p. 6); neither should it be stated that "the spleen shows little or no change in any of the stages of acquired syphilis" (p. 38); objections to Evans' red and gray types of acute splenic tumor (p. 17) and reticulo-endothelial system (p. 46) are not well taken. Granted the need for resurvey of some fields in the light of

latent Bartonella and other infections, still it is very doubtful if the suggestion will stand that the spleen is of little importance in the metabolism of iron, though essential in the utilization of copper. In a field where there is so much difference of opinion and observation, the paucity of such objections is in itself a tribute to the value of this text, which is to be welcomed as a very useful contribution.

E. K.

THE PROCEEDINGS OF THE CHARAKA CLUB. Vol. VIII. Post Multa Virtus Opere Laxare Solet. Pp. 202; illustrated. New York: Columbia University Press for the Charaka Club, 1935. Price, \$5.00.

THE anticipatory pleasure of opening a new volume from this unique club of medical literati is heightened by the four-year wait that has followed the appearance of its seventh volume. Nor could any one be disappointed. The twenty-five articles are supplemented by a list of sixty-three contributions given but not published. Most important, perhaps, is S. W. Lambert's "Reading from Vesalius" on vivisection (Bk. VII, Chap. 19), which gives not only a translation and a photograph copy of the whole chapter in the second edition, but a trenchant essay on Vesalius' physiologic knowledge and on the ethics of vivisection. Sachs' eulogy of G. D. Stewart, a deceased member of the club, is followed by several delightful lyrics by Stewart scattered through the volume. The versatility of the members, though producing too many and varied articles to be considered here, well support their motto, "Post multa virtus opere laxare solet."

E. K.

THE DEPOPULATION OF PACIFIC RACES. Bernice P. Bishop Museum Special Publication 23. By S. M. LAMBERT. Pp. 42; 11 illustrations, 19 tables. Honolulu: Bishop Museum Press, 1934. Price, \$1.00.

THIS study, conducted with the support of the Rockefeller Foundation, demonstrates that 1, in the Eastern Polynesian islands the native population has been reduced to a point that seems to preclude their racial regeneration; 2, the mixed native population of the mid-Pacific islands are safely on the upgrade, while, 3, the purely Melanesian islands of the west Pacific are still on the decline. The successful development of native practitioners in the Fiji and other mid-Pacific islands suggests that this may offer an important factor in the solution of the problem of racial regeneration.

E. K.

NEW BOOKS.

Lilly Research Laboratories—Dedication. Pp. 128; illustrated. Indianapolis: Eli Lilly & Co., 1934.

Nutrition and Disease. The Interaction of Clinical and Experimental Work. By EDWARD MELLANBY, M.D., F.R.C.P., F.R.S., Late Professor of Pharmacology, University of Sheffield; Consulting Physician, Royal Infirmary, Sheffield; Secretary of Medical Research Council. Pp. 171; illustrated. London: Oliver & Boyd, 1934. Price, 8/6.

Diet and Physical Efficiency. The Influence of Frequency of Meals Upon Physical Efficiency and Industrial Productivity. By HOWARD W. HAGGARD, M.D., and LEON A. GREENBERG, PH.D., of the Department of Applied Physiology in Yale University. Pp. 180; 31 illustrations and 35 tables. New Haven: Yale University Press, 1935. Price, \$3.00.

Lactobacillus Acidophilus and Its Therapeutic Application. By LEO F. RETTGER, PH.D., LL.D., Professor of Bacteriology in Yale University, MAURICE N. LEVY, M.D., Practising Physician, Bridgeport, Conn., LOUIS WEINSTEIN, PH.D., and JAMES E. WEISS, PH.D., Research Fellows in Yale University. Pp. 203. New Haven: Yale University Press, 1935. Price, \$2.50.

The Surgical Clinics of North America, Vol. 15, No. 3 (Chicago Number—June, 1935). Pp. 239; 119 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, Paper, \$12; Cloth, \$16.

This Chicago number offers 9 articles in a Fracture symposium and 12 others on a variety of topics by well-known surgeons.

Die Werke des Hippokrates. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würzburg. Book 6 (Price, Rm. 7.50), Luft, Wasser und Ortslage (Air, Waters and Places); Book 9 (Price, Rm. 7), Die Diät (Lebensordnung) in akuten Krankheiten (Diet in Acute Diseases). Book 6, pp. 84; illustrated. Book 9, pp. 95. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

Child Psychiatry. By LEO KANNER, M.D., Associate Professor of Psychiatry, The Johns Hopkins University. With Prefaces by ADOLF MEYER, M.D., LL.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University, and EDWARD A. PARK, M.D., Professor of Pediatrics, The Johns Hopkins University. Pp. 527. Springfield, Ill.: Charles C Thomas, 1935. Price, \$6.00.

Apparatus and Technique for Roentgenography of the Chest. By CHARLES WEYL, and S. REID WARREN, JR., Moore School of Electrical Engineering, University of Pennsylvania. Pp. 166; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, \$5.00.

The International Medical Annual. Fifty-Third Year, 1935. A Year Book of Treatment and Practitioner's Index. Editors: H. LETHEBY TIDY, M.A., M.D. (Oxon.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., with 31 Contributors. Pp. 522; 60 illustrations and 64 plates. Baltimore: Wm. Wood & Co., 1935. Price, \$6.00.

From "abdominal surgery" to "yellow fever" this useful annual made in Great Britain covers medical progress in 1934 in a very satisfactory manner.

The Medical Man and the Witch During the Renaissance. The Hideyo Noguchi Lectures. Third Series, Vol. 2 of the Publications of the Institute of the History of Medicine, The Johns Hopkins University. By GREGORY ZILBOORG, M.D., Pp. 215; illustrated. Baltimore: The Johns Hopkins Press, 1935. Price, \$2.50.

Vier Vorlesungen über Kreislauffragen. Gehalten an der spanischen Universidad International de Verano en Santander. By DR. BRUNO KISCH, Ordentlichem Professor der Physiologie an der Universität Köln. Pp. 64; 6 illustrations. Köln: Paul Kuschbert, 1934. Price, Rm. 3.60.

NEW EDITIONS.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D., (BERLIN), Director of the Medical Division, Bikur Cholim Hospital, Jerusalem, etc. Pp. 492; 168 illustrations. Third Edition Revised and Enlarged, Translated by CARL PRASNITZ, M.D., (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Honorary Research Fellow, Victoria University of Manchester, etc. Baltimore: William Wood & Co., 1935. Price, \$11.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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ARTERIOSCLEROSIS AND RHEUMATISM

Arterial Calcification Associated With Renal Disease. Calcification of the arteries arises under certain circumstances. The variety usually encountered is the calcification of the media of the peripheral arteries which goes by the name of Mönckeberg's sclerosis. On the other hand, calcification also occurs in the areas of atheroma of the intima, and appears to be a deposition of the calcium salts in relation to the presence of fatty acids or their salts. Virchow long ago encountered a number of cases of metastatic calcification of arteries and other tissues arising as a process secondary to extensive destruction of the bony tissues. This type of arterial calcification is quite unusual. On the other hand, there is also a variety of calcification affecting the arteries, which is based on faulty metabolism. Such cases are occasionally encountered in very young children in whom no obvious lesion accounts for the widespread deposition of calcium in the arteries.

Hesse¹ describes the case of a woman aged 29 years, who in childhood had suffered measles, scarlet fever, renal incompetency and anemia, and in whom the renal condition became progressively more severe. She suffered occasional attacks of angina and on such occasions the urinary findings showed an exacerbation of the kidney condition. At autopsy a generalized arteriosclerosis was encountered, the arteries being impregnated with a calcium deposit in the media. There was very little intimal change. This process of calcification affected the aorta and all of its branches even to the smaller visceral arterioles. The renal lesion was of the nature of glomerulonephritis with a great deal of contraction. The author, however, finding peculiar tubular changes, was inclined to believe that a congenital hypoplasia of the kidney had existed prior to the onset of the nephritis. In reviewing the description of these organs we cannot feel convinced in this latter interpretation.

It would appear that in this case the renal lesion was associated with an altered metabolism of calcium or a change in the secretory ability

of the kidney for calcium. There are no studies available to indicate whether this patient suffered from a hypercalcemia during life. The case, however, illustrates the development of calcareous deposits in the arteries under conditions of renal insufficiency.

Arteriosclerosis of the Arteries of the Tongue. In the many studies on the distribution of arteriosclerosis, evidence is available on the incidence of the condition in almost every artery of the body. Thiessenhusen,² however, points out that no contribution is available dealing with the presence of arteriosclerosis in the arteries of the tongue. He undertook an examination of a series of cases in which the lingual artery and its branches were dissected out and the character and distribution were noted. Some interesting facts arose in this investigation. The author points out that the muscles of the tongue are probably in greater activity through life than any other muscle group. The lingual arteries continue to develop and increase in thickness of the media up to 20 years; from then on until the fifth decade the arteries remain fairly constant in their size; after the fifth decade the media again begins to increase its diameter. The intima varies greatly in thickness, sometimes showing some diffuse thickening, at other times showing nodules. This intimal change is not accompanied with the deposition of fat and is not of the nature of atherosclerosis. It appears to resemble the hyperplastic overgrowth of the intima in which the elastic fibers increase in number. He noted that the internal elastic lamina from 5 years onward always showed more or less splitting. Furthermore, after the age of 29 there was a deposition of calcium in some portion of the elastic fiber; with age this deposition increased until the vessel was completely encircled by a calcareous ring. Not uncommonly an extensive calcification of the internal elastic lamina was unaccompanied by other changes in the intima. The author is unable to offer any explanation for this curious arterial change unless it is assumed that through the activity of the artery the elastic fibers suffer certain chemical and physical changes allowing the deposition of calcareous granules.

The Relation of Atherosclerosis of the Abdominal Aorta, the Carotids and the Carotid Sinus to Rheumatic Fever. The initiative for this pathologic study arose through the discussion by Weil at the recent Utrecht Conference, in which he indicated that a very large proportion of disease conditions in man had their origin in rheumatic infections. This again gave rise to the controversy, as to what shall be determined as rheumatic. Clinically it is very difficult to make a clear differentiation by symptoms alone, while the laboratory tests during life are still insecure. The pathologist, however, has the opportunity of utilizing a criterion, which is fairly satisfactory for determining the rheumatic condition, by the Aschoff nodule. In general the authors are agreed that this curious reaction arising in the various tissues of the body is distinctive for the rheumatic state. A difficulty, however, does present itself in accurately defining the Aschoff nodule. Gigante,³ working under the direction of Aschoff at Freiburg, studied a series of arteries to determine a relationship between rheumatic disease and atherosclerosis. The investigation was particularly directed to an analysis of the abdominal aorta, the carotid arteries and the carotid sinus. The attack by rheumatism upon the ascending limb of the aorta with the development of nodular reactions, like Aschoff nodules in the adventitia

and the media, has been demonstrated by Klotz, Pappenheimer and others. It has always been claimed that the rheumatic lesion selects the ascending limb of the aorta and that its presence in the abdominal aorta was unusual. Subsequently Klinge claimed to have found the lesion not uncommonly in the abdominal aorta and associated with the development of atherosclerosis. Gigante studied 30 cases ranging in ages from 26 to 81 years, who died from a variety of conditions, some of whom had an antecedent history of rheumatic fever. He has failed to discover a single rheumatic nodule in the abdominal aorta, the carotid artery or the carotid sinus. He lays particular emphasis upon the negative findings in the vessels in a case in which the myocardium was thickly seeded with typical rheumatic nodules. Furthermore, he has failed to discover specific types of searing which might have resulted from previous rheumatic involvement. Many of the arteries showed typical atherosclerosis of the intima and not uncommonly these intimal lesions were associated with a vascularization of the media immediately opposite to them. However, he notes that this vascularization appears in the vascular wall of rheumatic and non-rheumatic cases indifferently. The presence of advancing capillaries from the adventitia through the media towards the intima takes place whenever a severe nodular process arises in the intima, but the author could find no correlation of this response to the presence of a rheumatic condition in the individual. The author also comments upon the finding of non-specific reactions with lymphocytic infiltration following the course of the capillaries in the adventitia and media. These lymphocytic aggregations seem to have no relation to any particular condition in the individual. He indicates that their presence must not be confused with the true Aschoff nodule.

Acute Rheumatism. A group of British investigators undertook to evaluate the importance of some of the etiologic factors of rheumatism which have been advanced by others. In speaking of rheumatism they refer to acute rheumatic fever. Recent years have emphasized the importance of a group of streptococci in the precipitation of an attack of rheumatic fever. It soon became apparent that the streptococci, which were found in the upper respiratory tract in this disease, did not fall into a single cultural class, although they possessed immunologic similarity by which they were identified. Many have not been satisfied with the evidence incriminating the streptococcus as the causal agent of rheumatic fever, and have indicated in support of their contention the want of uniform findings during the acute phase of the rheumatic disease. Distinction must be made between the acute tonsillitis and the rheumatic attack which follows after an interval. It was this interval or "silent interval" which attracted the attention of the British workers. Schlesinger and Signy⁴ pointed out that usually a silent period of from 10 to 21 days intervened between the rheumatic relapses and the tonsillitis or pharyngitis, which almost invariably preceded them. In a later communication⁵ these authors have revised the length of the silent period to 2 to 4 weeks. It is during this silent period that certain events are taking place, some of which may be detected by serologic methods. During this period, these authors have found that there is a specific precipitin reaction demonstrable by the addition of the patient's serum to an antigen prepared from strains of

streptococci. All strains of streptococci do not serve for the production of this antigen. The nuclear protein of a hemolytic strain of streptococci isolated from the throat of a rheumatic case appears to give the best results. Nevertheless on continued cultivation of these streptococci the antigenic properties rapidly diminished. Other strains of hemolytic streptococci such as those isolated from strains of scarlet fever or from cases of non-rheumatic tonsillitis are not as valuable for antigen in the precipitin test. The authors also studied the value of the globulin and albumin fractions from these streptococci for their antigenic properties. In studying the series of rheumatic patients in respect to the precipitin reactions the authors made some interesting observations. The precipitin response appeared shortly after the development of the tonsillitis or pharyngitis and increased in intensity for a period of 3 or 4 weeks, although a number had their highest titer at a little later period. The reaction appeared to be directly related to the streptococcic infection of the throat and bore no relation to the intensity of the rheumatic manifestations which appear subsequently. It was noted that the height of the precipitin reaction determined the time of onset of the rheumatic attack; in other words it appeared that the immunologic response to the presence of the sore throat induced by a special variety of streptococcus was the warning of the onset of a new group of symptoms recognized as rheumatic fever. From this finding the authors suggest that the streptococcus plays a part in increasing the susceptibility of the individual to some other agent which initiates the rheumatic disease. The authors have studied many controls including cases of scarlet fever, non-rheumatic tonsillitis, subacute bacterial endocarditis and other streptococcal conditions. A certain number of these gave rise to a precipitin reaction not unlike that in rheumatic fever. The significance of this is yet to be determined. The authors have also utilized antigens of other bacteria in relation to the production of a precipitin by the serum of rheumatic cases. It is interesting that with antigens of some bacteria, especially staphylococci, a common precipitin response is present both in the normal controls and in the rheumatic cases. As the investigations by these authors have led them to believe that an important other factor attacks these individuals with specific immunologic reactions, they have then turned to a search for such an agent. Their attention was drawn to the possibility of a virus, having symbiotic relations to the streptococcus.

The virus nature of the infection in rheumatic fever has been referred to by a number of authors since Vecchi first claimed to have found positive results in animal inoculation with bacteria-free filtrates (1912). The proof of the presence of a virus has not been entirely satisfactory and it has been contended that the type of experimental animal used accounted for the failure. Animals do not develop rheumatic fever in their ordinary life, while the usual laboratory animals appear to be quite indifferent to a number of infectious agents affecting man. The British authors, Schlesinger, Signy, Amies and Barnard,⁶ utilized pericardial fluids of rheumatic cases which, when subjected to high speed centrifugation gave rise to a small precipitate which was analyzed in several ways. The sterility of the fluids was determined by cultural methods. Microscopic examination using the dark field method and with a magnification of 1000 diameters showed the presence of numerous

particles which could not be analyzed directly under the eye. A staining technique along with Barnard's method of illumination showed the presence of many particles of uniform character besides other indifferent masses. Such particles were not present in control fluids. They believe these particles represent the elementary bodies of some virus. Furthermore, they have also found that these small bodies are agglutinated by the sera of patients suffering from acute rheumatic fever and who are resisting the further progress of the disease. The sera of rheumatic patients in the quiescent stage failed to show an agglutination. Negative results were also obtained with the sera of normal patients and with patients suffering from non-rheumatic infections. The authors recognize the importance of the streptococcal infection as a factor in the etiology of the disease. It is suggested that the lowered resistance produced by such infections enables the virus to enter the body, or, if the virus is already lying latent in the tissues, allows it to assume active characters.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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BRUCELLOSIS

BRUCELLOSIS (the most recent name for undulant fever, Malta fever and Mediterranean fever) is one of our newer problems in clinical and preventive medicine so far as concerns much of the world. Until approximately 10 years ago the disease was looked upon as confined exclusively, or almost exclusively, to the Mediterranean basin. Then came the work of Evans and others, showing that the disease was much more prevalent than had been recognized and, indeed, might be expected to occur any time in any part of the world. About 2000 cases are

reported annually in the United States but doubtless many are missed. Early in the history of the disease the clinical course was recognized as being varied, and erroneous diagnoses were the rule rather than the exception. Perhaps the most frequent mistake lay in designating undulant fever as influenza, but Evans mentions the disease being mistaken for "typhoid, malaria, rheumatic fever, endocarditis, tuberculosis, bronchial pneumonia and bronchitis." Erroneous diagnoses were perhaps to be expected even in connection with the relatively acute cases. It is therefore not in the least surprising to find that such diagnoses have been even more common in connection with cases of long duration. Because of its low mortality rate, undulant fever is not considered a major public health problem, but the disease produces in many cases such prolonged, debilitating symptoms, that it should warrant the serious consideration of health officers everywhere.

In this country the usual source of infection is lower animals (particularly cattle and hogs) infected with the organism of contagious abortion. Infection by contact with cases of the disease in man is practically unknown and the patient need not be regarded as a source of danger.

Hardy² notes particularly the exceptional risk to packing-house employees, who, while furnishing but 0.1% of the population of Iowa, supply 10% of the cases of undulant fever. Infected swine are a more serious source of danger than infected cattle.

There are at present three recognized types of infecting organisms of the *Brucella* group. These types are associated characteristically with goats, cattle and swine, respectively. Any one of the types may, however, infect any species of animal.

The bacteriologic history is interesting. First, Bruce identified an organism as the cause of undulant fever in man; then Bang established an organism as the cause of contagious abortion in domestic animals, but those working with the two organisms in human and veterinary fields, respectively, failed to note the great similarity—indeed, the practical identity—of the organism of undulant fever in the human and of contagious abortion of farm animals. The work of Evans established the fact that for practical purposes the organisms from the two sources may be regarded as identical, and led to the relating of many cases of the disease in man to disease of cattle and swine. The relation of the disease in goats to that of man had already been established.

In general, it may be said that the pathogenicity for man is markedly less in the *abortus* type (that derived from cattle) than in either the *suis* or *mclitensis* types (derived from swine or goats). However, it is possible to get a strain conforming to almost any type from almost any host.

It has long been known that arthritis and orchitis are common complications and sequelæ of brucellosis. Recently, Hardy² reported what appeared to be hitherto unrecognized complications, namely: meningitis, osteomyelitis, spondylitis and pleurisy with effusion.

Evans¹ believes that many long-standing cases are overlooked. It has been estimated that perhaps not more than 20% of cases are diagnosed correctly even when circumstances suggest the true nature of the condition; in cases with less obvious history of contact the percentage of cases diagnosed correctly must be very small. Evans refers

particularly to the misleading nature of the term "undulant fever," and notes: "There is to be found in the literature little information about the disabling chronic form of the disease in which, during long periods of many months of illness, there may never be a significant rise in temperature." Evans believes that many cases of chronic brucellosis are diagnosed incorrectly as neurasthenia, and considers as probable manifestations of chronic brucellosis the symptoms often attributed to a neurologic condition—"exhaustion, insomnia, irritability, and complaints of aches and pains for which no objective sign can be found." She suggests that before a case is labeled "neurasthenia," brucellosis should be excluded.

The diagnosis in chronic cases is difficult. Cultivation of the causative organism from the blood stream, so valuable in the diagnosis of acute cases, rarely is accomplished in the chronic cases. The agglutination test may give misleading negative results. A positive reaction by this test is highly significant but occasionally healthy individuals give a positive reaction, presumably due to subclinical infection with *Brucella* organisms. The skin test has not been used sufficiently in general practice to determine its utility.

There is enough evidence to indicate that the physician is likely to overlook brucellosis unless he is alert to the possibility of its existence when confronted with symptoms suggesting a variety of clinical conditions, acute or chronic.

In general, there are two important modes of transmission³ but the relative frequency of infection by these cannot be determined accurately at the present time. First, we have contact of man with infected animals or animal products; this mode of infection is particularly common among butchers, veterinary surgeons, sausage makers and agriculturalists. Second is to be considered the possibility of infection from milk of infected animals. Classically, the milk of the goat is the source of infection, but the goat is of minor importance as a cause of undulant fever in the United States, save in the restricted area in the southwestern part of the country where goats are used to some extent to provide milk for human use. Milk from infected cattle causes many cases—just how many remains to be determined. It is rather significant that the disease is practically unknown in communities where pasteurization of milk is strictly carried out. The disease is widely recognized as likely to be contracted by those who carry on experimental investigations in the laboratory, and some authors make a separate group for cases of this type.

It is obvious that in the final analysis the eradication of this disease becomes a problem for the veterinary scientists, since infected domestic animals always constitute the ultimate source from which the disease is derived.

Not only are definitely diseased animals sources of infection but, according to Carpenter and Boak,⁴ apparently normal animals may also carry the infecting organism.

Measures for the eradication of the disease from herds of cattle center around the elimination of animals shown by the agglutination test to be infected. In a number of States campaigns of this sort are under way, but it is too early to predict the effect these efforts may have on the public health aspects of the problem. In the meantime, until

those working in the field of animal pathology establish the final solution of this problem, steps may be taken that will obviate the occurrence of many cases. When milk is the source of the infection the easiest and simplest procedure is the requirement of pasteurization or, if this proves impracticable, boiling of the milk will serve equally well. Cases originating from contact theoretically are preventable by scrupulous care in the handling of infected animals or animal products. The use of rubber gloves would seem to offer satisfactory means of protection, although it must be admitted that we are not acquainted with any practical experience to confirm this.

With respect to treatment but little is to be said. The majority of cases may be expected to recover spontaneously within a month to 3 months—a few drag out indefinitely. Chemotherapy has been tried extensively and generally has not given results that are encouraging. Certain advocates of vaccine therapy have reported astonishingly good results; nevertheless, in the hands of others vaccines have failed.

G. W. McCoy, M.D.

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PATHOLOGIC AND IMMUNOLOGIC PROBLEMS IN THE VIRUS
FIELD.*

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THE nature of this symposium requires discussion of both pathologic and immunologic phenomena associated with virus diseases. I shall also call attention to certain problems undergoing or awaiting solution in this field.

Viruses or filterable viruses were first shown to exist and are still principally recognized clinically and experimentally by means of their activity in a host. Therefore, I shall begin this talk by describing certain pathologic phenomena and discussing their significance.

When the pathology of virus diseases is mentioned, it is customary for the question of inclusion bodies to arise immediately. These bodies are not necessarily the most significant feature of the pathologic changes seen in tissues affected by viruses. Nevertheless, it seems advisable to dispose of them before going to phenomena of greater significance.

In many, but not all virus diseases, significant intracellular changes spoken of as inclusion bodies have been described. Some of the changes were recognized many years ago; Paterson, for instance, described molluscum corpuscles in 1841.

Most workers now admit that inclusion bodies are significant and

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rarely exist in the absence of the activity of a virus. The nature of all of these bodies is not known. For example, the nuclear inclusions found in herpes febrilis, herpes zoster, varicella, Virus III infections in rabbits, yellow fever, guinea pig salivary gland disease, equine encephalomyelitis, pseudorabies, and B virus disease, are still a source of differences of opinion. On the other hand, within recent years there has been a certain amount of crystallization of opinion in regard to some of the cytoplasmic inclusions.

In 1873, Bollinger found large cytoplasmic inclusions in cells infected with fowl pox virus, and, in 1892, Guarnieri found similar inclusions in the cytoplasm of cells affected by vaccinia. In 1904, Borrel observed minute coccoid bodies in smears made from fowl pox lesions. Similar bodies were observed in 1906 by Paschen in smears of material from vaccinal lesions. For a long time many workers either denied the existence of all these bodies or failed to grasp their significance. The recent work of Goodpasture,¹ Ledingham,² Craigie,³ and others, however, has clearly established the fact that these minute bodies, approximately 150 to 175m μ in diameter and invisible by means of ordinary light, either represent the viruses of fowl pox and vaccinia or are intimately associated with the active agents inciting the diseases. Furthermore, it appears that the Bollinger and Guarnieri bodies are composed chiefly of aggregates of the minute coccoid structures.

The minute forms under discussion are usually spoken of as elementary bodies and play an important rôle in diseases other than fowl pox and vaccinia,¹ for example infectious ectromelia of mice, psittacosis, smallpox, canary pox and probably other pox maladies. The exact nature of elementary bodies is not known. Nevertheless, they have played an important part in recent immunologic and serologic studies of vaccinia.

Minute structures similar to elementary bodies have been described as occurring in smears containing the active agents of foot-and-mouth disease and bacteriophagy. Much doubt naturally exists in regard to the importance of such structures, because the active agents of these diseases (foot-and-mouth disease virus being 8 to 12m μ in diameter) are so small that it is hardly conceivable that they can be made visible by mordants and stains. Moreover, it is wise to suspend judgment of Ledingham and Gye's⁴ recent report on elementary bodies in association with the viruses causing filterable tumors in chickens.

Viruses seem to be obligate parasites, requiring an association with susceptible cells for multiplication. Consequently, it is not unreasonable to suppose that their relation to host cells and the reaction of these to their presence and activity should result in phenomena of importance and significance. In the case of certain viruses, inclusion bodies represent one of the phenomena resulting from such an association. Although the inclusion bodies have

attracted a great deal of attention in the past and have caused an untold amount of discussion, I believe that there are certain reactions of tissues to viruses, so obvious that they are ignored, which are of more fundamental importance than are the inclusion bodies themselves. I refer to proliferation, proliferation followed by necrosis, and necrosis, changes which give to the lesions their pathognomonic characters. In 1928, I⁵ wrote at length concerning these reactions and since that time other workers, *e. g.*, Goodpasture,⁶ Shope,⁷ Andrewes⁸ and Rous and Beard⁹ have expressed opinions about the matter. In view of the fact that many virus diseases are acute infections, one doubtless wonders what part I consider inflammation to play in the pathologic pictures. Inflammation in virus maladies is a secondary phenomenon while hyperplasia and necrosis of the affected cells are the primary, most important, and most characteristic reactions of cells to this type of infection.

The following brief description seems to portray with a reasonable amount of accuracy what actually occurs when viruses attack their hosts. These highly parasitic agents multiply on or in susceptible cells and cause symptoms and signs of disease only when they come in contact with such cells. If the action of the viruses is not extremely rapid and explosive, and if the susceptible cells are capable of multiplication, the primary effect of the active agents is stimulation leading to cellular hyperplasia. Following the hyperplasia there is usually a destruction or necrosis of the cells which in turn is attended or followed by a secondary inflammation representing the reaction of the neighboring tissues and of the host. The balance between the stimulative and destructive tendencies of the viruses determines whether hyperplasia or necrosis is the predominant part of the pathologic picture. Thus, in some virus diseases, for example, vaccinia, varicella, smallpox, and fever blisters, vesicles (*i. e.*, necrosis) occur; in others, *e. g.*, warts and tumors, an overgrowth of tissue is the predominant feature. When vaccinia, smallpox, and fowl pox are mentioned, one usually visualizes vesicles and pustules. Nevertheless, in these maladies a hyperplasia of cells precedes the formation of vesicles. This fact is beautifully illustrated by sections prepared at the proper time from young fowl pox lesions or from rabbit corneas infected with vaccine virus or the virus of smallpox. If the action of the viruses is explosive or rapid, as for instance in yellow fever and Rift Valley fever, or if the susceptible cells are incapable of division and multiplication, as is the case with nerve cells, then the primary pathologic changes are necrobiosis and lysis of cells. The destruction of Purkinje cells¹⁰ in the cerebellum of a monkey with louping ill is a striking example of the lysis of cells by viruses.

From what has been said it is obvious that viruses will enter into any discussion of the etiology of tumors and malignant growths. If one resists the temptation to split hairs, one must admit that

some tumors are caused by viruses. If one desires to split hairs, however, one can say that Rous' sarcomata and Shope's papilloma do not represent tumors but examples of virus hyperplasia. Regardless of what these disease processes are called, they still exist and must be recognized.

Granted that viruses produce growths having the characters of tumors, one is faced with the question, do viruses produce all tumors? Of course such a question cannot be answered at the present time. My guess is—and everyone working with viruses and tumors is entitled to a guess—my guess, then, is that tumors may arise as the result of more than one mechanism. Though Rous and Beard¹¹ have shown that the Shope papilloma has the immediate traits of a tumor and that in many instances this tumor undergoes malignant changes occurring in carcinomas, yet the facts are still open to several interpretations: 1, Both the benign papilloma and the malignant growth that sometimes supervenes after months may be caused by the same virus, a conditioning of the host cells having taken place in certain instances that permits an altered or malignant type of reaction to the virus instead of the papillomatous one that usually occurs. 2, The virus ordinarily producing the papilloma may undergo a change itself that enables it to cause a malignant growth instead of a benign papilloma. 3, The papilloma and the intercurrent bacterial infection that frequently accompanies many of the lesions may act as excellent highly specialized chronic irritants and as such induce malignant changes in the cells of the rabbit in a manner similar to that of repeated applications of tar to the skin. Interpretations one and two emphasize the presence and activity of a virus. On either assumption the malignant process would regress and disappear if the virus were removed from the body. In the third interpretation emphasis is placed on some change that occurs in the cells and is reflected in or inherited by daughter cells. Therefore, once such a change has occurred in the cells, the removal of the virus from the body would not influence the progress of the malignant growth any more than does a cessation of tarring lead to a cure of the malignant growth resulting from it.

At the moment it would be futile to pursue this matter further. Nevertheless, hyperplasia and necrosis are such important phenomena in the pathologic pictures produced by viruses that pertinent remarks had to be made concerning them if for no other reason than to show that such disease processes as tumors, warts, measles, fever blisters, smallpox, poliomyelitis, and bacteriophagy possess characteristic pathologic pictures in common in spite of the fact that they exhibit striking clinical differences.

Now we shall consider for a moment certain interesting immunologic problems encountered in the virus field. The active agents under discussion are undoubtedly antigenic, and, because of this fact, they should be of interest to immunologists. It has been shown

that agglutinins, precipitins, complement-fixing antibodies and neutralizing or protective antibodies may appear in the sera of individuals who have recovered from certain virus diseases. Moreover, an obvious infection with a virus usually leads to a state of increased resistance in the recovered host to further molestation by the same agent. It is of no particular interest, however, that such things take place in virus diseases, because they are known to occur in other types of infection. Nevertheless, there are some facts of particular interest which deserve consideration at this time.

- 1, Why is it so difficult to obtain an efficient immunity against virus infections by means of injections of vaccines composed of inactivated viruses?
- 2, Are the agglutinins, precipitins, complement-fixing antibodies, and protective antibodies the result of the stimulation of a host by means of a single antigen? If not, do the different antigens represent different fractions of the virus, or do some of the antigens arise in the host as a result of infection?
- 3, In what manner do the neutralizing or protective antibodies act?
- 4, Finally, why do so many virus diseases lead to a permanent immunity in recovered hosts?

Questions arising in regard to the immunization of individuals with inactive viruses are difficult to answer, because it is almost impossible at present to determine when a virus has been completely inactivated. For example, Lippert¹² doubts whether Perdrau and Todd by means of methylene blue and light completely inactivated the canine distemper virus which later was shown to immunize dogs against distemper. Further, Dunkin and Laidlaw have shown that formalized canine distemper virus will produce a fleeting immunity in vaccinated dogs, but in order to get a solid lasting resistance active virus must be employed. Certain workers are of the opinion that the amount of inactive virus is the all important factor *i. e.*, if a sufficient amount were used, a solid immunity would result. Mackenzie¹³ reported that with small doses of inactive Rift Valley fever virus he was unable to immunize mice, while with large doses, 1 cc. administered intraperitoneally, he was able to establish a good resistance in the animals to the active agent. Assuming that the virus was completely inactivated and that the mice were solidly protected, one must remember that a mouse weighs in the neighborhood of 20 gm. and that 1 cc. or 1 gm. of the virus emulsion was administered, *i. e.*, approximately $\frac{1}{20}$ of the body weight. On the basis of these figures a man weighing 150 pounds would require $7\frac{1}{2}$ pounds of vaccine—not a very practical procedure. When one brings up the question of the production of immunity by an inactive virus, antirabic vaccination is cited as an example of protection induced in this manner. I am glad to find, however, that some workers, for example Webster and Dawson,¹⁴ are no longer willing to accept dogmatic statements handed down to them in regard to antirabic vaccination, but insist upon exploring the field for themselves.

Whatever viruses may be, in an active state they are antigens, and as such one would like to think of them as containing proteins, or at least as being linked in some way to proteins. Therefore, if sufficient amounts of these agents in an inactive state, yet with their antigenic components not altered by inactivation, were administered to subjects in the form of vaccines, I would not be surprised to find complement-fixing antibodies, etc., appearing in the sera of vaccinated individuals, nor would I be disturbed to find that a certain amount of resistance to infection had resulted. In the past, however, it has not been possible to obtain viruses in sufficient amounts in a relatively pure state to determine what happens to their antigenic components when inactivated. Recently, Craigie^{3,15} has opened up this field in regard to vaccinia and has found that vaccine virus is composed of several antigens some of which are extremely labile and appear to function in the production of resistance, while others are stable and induce the formation of agglutinins, etc. Parker,¹⁶ working in my laboratory, has confirmed many of Craigie's findings. What Craigie has accomplished for vaccinia must be done with other maladies, and, in the meantime, generalizations should be suspended.

For the sake of argument let us assume that it has been demonstrated that a certain degree of immunity can be obtained by completely inactive virus, provided sufficient amounts are administered. What about the duration of the protection induced in this manner? All the evidence at hand seems to indicate that whatever protection is produced in this way endures only for a relatively short time. Strange to say, many workers do not seem to be disturbed by this fact. In the case of hogs and cattle that are raised for the meat market and will live for a short time only, it is not necessary to produce a lasting immunity. Nevertheless, the duration of an immunity produced by vaccines, particularly when the vaccines are expensive to make and difficult to administer, is of great importance in the protection of human beings against smallpox, yellow fever, measles, poliomyelitis, etc.

As I have already indicated, some of the viruses at least are probably made up of several antigenic components which function differently in the process of immunity. Now we would like to know whether all the antigens active in virus diseases are found in the viruses themselves. Several workers have raised this question, and Hughes¹⁷ has brought some evidence to show that the precipitinogen found in the blood and tissues infected with yellow fever virus is not a part of the virus but arises in the host as a result of the infection. Furthermore, in view of the fact that it is difficult, and according to some workers impossible to demonstrate a union between certain viruses and their neutralizing antibodies, Sabin¹⁸ has suggested that the antigens causing the production of neutralizing antibodies do not exist in the viruses but arise from the infected

host. This idea while interesting has as yet no definite experimental confirmation.

An appropriate amount of serum from a host recovered from a virus disease mixed with the homologous virus usually results in what is called a neutral mixture, *i. e.*, the mixture of virus and convalescent serum does not produce evidences of disease in a susceptible host. Because of this phenomenon workers have developed the habit of speaking of the virucidal action of convalescent serum. From the remarks that follow it will become obvious that "virucidal" is not the proper word to use in this connection.

Bedson,¹⁹ Todd,²⁰ Andrewes,²¹ Sabin²² and others have shown by means of dilution, filtration, and ultracentrifugation that the viruses in the neutral mixtures spoken of above are not killed or inactivated. In fact, an abundance of active virus has been recovered from such mixtures. Moreover, certain investigators contend that contact of the viruses with immune sera *in vitro* for a number of days does not result either in their inactivation or in a union of them with the neutralizing or protective antibodies. Other workers, however, are of the opinion that union and inactivation finally occur under such circumstances.^{19,23,24}

In spite of the fact that the question regarding the final union *in vitro* of viruses with the protective antibodies has not been settled, most workers are agreed that the viruses in the so-called neutral mixtures which are usually injected into animals shortly after preparation are not really dead or inactive. Further evidence in regard to this matter is obtained from Green's²⁵ *in vivo* experiments on fox encephalitis in which he found that most foxes receiving neutral mixtures do not become sick, but that in a certain percentage of the animals a typical disease occurs after a very long incubation period. A similar state of affairs has also been noted in work on poliomyelitis and has been interpreted as an indication that the virus in the neutral mixtures is not killed or inactivated, but is only held at bay for a time by the immune serum.

The facts related above are interesting, and one naturally desires to know why the mixtures of convalescent sera and viruses do not usually produce disease even though the viruses are still active. Several years ago we²⁶ attempted to throw light on the subject by the investigation of some of the phenomena in tissue cultures. As a result of this work we were able to show that typical vaccinal lesions developed in tissues that were exposed to vaccine virus for a short time and then cultivated in potent antivaccinal plasma. Furthermore, active vaccine virus was demonstrated in these cultures in spite of the immune plasma. In other words, immune plasma and normal cells did not inactivate vaccine virus. We went still further and showed that vaccine virus was not inactivated in cultures composed of immune cells, immune plasma, and virus.

Simultaneously with us, Andrewes²⁷ working with Virus III and herpes virus, and more recently Downie and McGaughy²⁸ working with infectious ectromelia, and Sabin¹⁸ working with pseudorabies, herpes virus, and B virus have obtained similar if not identical results.

The facts that some viruses are not inactivated or killed either by mixtures of normal cells and immune serum or plasma or by mixture of immune cells and immune plasma or serum, are substantiated by the *in vivo* experiments of Tulloch²⁹ and Downie.²⁸ The former injected vaccine virus into the testicle of a passively immunized rabbit. No evidence of infection occurred, but 7 days later active vaccine virus was recovered from the normal-looking organ. The latter worker injected the virus of infectious ectromelia into an actively immune mouse and recovered active virus from the serum of the animal several days later.

From what has been said it is obvious that the manner in which the protective or neutralizing antibodies act is not definitely known. It is also evident that this is a very attractive field for further investigations.

It is well recognized that recovery from a virus infection is usually followed by an enduring immunity. In many instances the immunity is operative during the remainder of an individual's life. Of course there are exceptions to the rule. For example, common colds recur repeatedly in the same individual, and herpes simplex or fever blisters occur at frequent intervals in the same subjects. The persistence of immunity in hosts recovered from virus diseases is so striking that it is not surprising that an explanation of the phenomenon has been sought. Furthermore, if it is the rule to encounter a lasting immunity in virus diseases, one would like to know the reason for the exceptions.

In the case of poliomyelitis and measles, the viruses of which one encounters from time to time throughout life, one might explain the persistent immunity and the presence of neutralizing antibodies on the basis of repeated contacts with the active agents. On the other hand, it is impossible to explain in such a manner the enduring immunity to yellow fever, which is accompanied by the presence of humoral antibodies, in individuals who have been out of yellow fever zones for periods of 25 to 50 years.

In view of the facts mentioned above, and because it is known that a refractory state to some bacterial and spirochetal diseases is associated with a persistence of these agents in the hosts, it has been suggested by a number of workers that at least in certain instances the protracted immunity following virus diseases is due to a prolonged or a persistent sojourn of the viruses in hosts once infected. This persistence of the viruses does not indicate that the hosts are capable of spreading disease.

Before proceeding, it is necessary for me to cite a few instances

in which it has been definitely established that viruses persist in immune subjects. Once a guinea pig is infected with the salivary gland disease virus³⁰ it becomes immune and retains its immunity, yet the active agent can be recovered at any time from its salivary gland. Dr. Pearce and I³¹ showed that Virus III is regularly carried by the Brown-Pearce carcinoma of rabbits and that rabbits inoculated with the tumor become immune to Virus III and exhibit neutralizing antibodies in their sera within 2 weeks after inoculation. Nevertheless, we were able to recover Virus III from metastases of the tumor removed several months after the animals had become immune to the virus. We also showed that vaccine virus persisted in the tumor for at least 2 months in spite of the fact that the rabbits harboring the new growth were refractory to the virus and possessed protective antibodies in their sera. The Rous virus is readily obtainable from tumors removed from chickens possessing humoral antibodies. Dr. Berry and I³² demonstrated the virus of psittacosis in a parrot that had had no contact with other birds for a period of 18 months. Furthermore, this bird was the source of virus that caused the death of a human being. Meyer and Eddie³³ have shown that psittacosis virus persists for a long time in immune mice that have recovered from the disease. The virus of laryngotracheitis³⁴ can be recovered from immune birds. Theiler³⁵ working with an encephalomyelitis that occurs naturally in mice has been able to obtain the virus from the cords of mice 1 year after the animals have recovered from the disease. In this connection the findings of Price recorded by Kunkel³⁶ regarding ring spot in tobacco are pertinent. When plants are inoculated with the virus they suffer an acute attack of the disease. "A systemic form of infection follows the development of primary lesions. Plants regularly recover and are then immune. They never suffer a second attack. The virus is retained by and recoverable from all plants which have had the disease."

Sufficient examples have been cited to show that viruses can and do persist in immune hosts. Moreover, failure to recover them from immune hosts is not necessarily positive evidence that they are not present.

In what way is it possible for viruses to persist in an immune host? It is most likely that these agents are intracellular parasites, and as long as they remain situated within living cells are in no danger of being eliminated from the body. If they do not kill the host cells, they can multiply and pass into daughter host cells. In this manner it is possible for them to remain indefinitely in an immune host. Such is undoubtedly what happens in the case of the Rous tumor.

At this point it is well to speak of the apparent lack of a lasting immunity to fever blisters. This disease is particularly interesting because the individuals who have recurring attacks possess an

abundance of neutralizing antibodies in their sera. The paradox has been explained on the basis of the persistence of the virus in the cells of immune individuals who develop crops of blisters whenever subjected to the conditions that are encountered as the result of typhoid vaccination, common colds, and exposures to high temperatures for several hours, etc.

Why does one fail to develop a permanent immunity to common colds? I do not know. It is interesting to speculate, however. The cold virus may be unable to establish itself permanently in the host, it may act in a manner similar to that of fever blister virus, or the superficial nature of the infection caused by it may have something to do with the poor development of immunity. In connection with the last possibility, investigators should become familiar with Tyzzer's³⁷ work on coccidiosis in gallinaceous birds.

In conclusion, it can be stated that there is no definite reason as yet to believe that the general principles of immunity, many of which are not known or understood, fail to operate in the virus field. Most of the immunologic and serologic oddities encountered in this domain apparently can be accounted for either by the intimate type of parasitism exhibited by the viruses or by the multiplicity and lability of antigens involved.

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(Titles have been omitted for sake of brevity.)

THE SEROLOGIC CLASSIFICATION OF HEMOLYTIC STREPTOCOCCI IN RELATION TO EPIDEMIOLOGIC PROBLEMS.*

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THE object of this communication is to demonstrate the application of recently perfected serologic methods in the epidemiologic study of *Strep. hæmolyticus* infections in limited populations.

Much of the earlier work on the subclassification of *Strep. hæmolyticus* was directed toward the establishment of specific pathogenicity. Thus many workers sought to establish differential characteristics which would enable them to distinguish between strains believed to be the specific etiologic agents involved in various diseases. For example, at one time it was thought that certain strains of *Strep. hæmolyticus* were specifically responsible for erysipelas, others for scarlet fever and that still others caused septic sore throat. This conception was the natural development of findings in the typhoid-paratyphoid group of bacteria where specific pathogenesis could generally be correlated with biochemical and serologic characteristics of the microorganisms.

No satisfactory classification of the hemolytic streptococci on this basis has as yet been proposed. Indeed, it is evident from many recent studies that any one of these infections, although a characteristic clinical entity, may be associated in different individuals with entirely distinct strains of *Strep. hæmolyticus*. Similarly, it has been amply demonstrated that the same strain may in different

* Presented, May 8, 1935, at the Fiftieth Annual Meeting of the Association of American Physicians, Atlantic City, N. J.

patients be associated with entirely different clinical manifestations, ranging from generalized infections on the one hand to simple pharyngitis on the other.

Lancefield¹ has shown that hemolytic streptococci can be differentiated serologically by means of the precipitin reaction into distinct and sharply defined groups. The method is relatively simple and gives results which are strikingly uniform and constant. It is based on the fact that the strains of each group contain a common specific carbohydrate, the so-called "C" substance. These groups, designated by the letters "A," "B," "C," etc., are shown in Table 1, together with the information now available as to the natural habitats of the members of these groups.

TABLE 1.—CURRENTLY IDENTIFIED SEROLOGIC GROUPS OF HEMOLYTIC STREPTOCOCCI.^{1,5}

Group.	Probable normal habitat.	Probable secondary habitats.	
		Associated with infections.	Not associated with infections.
A . .	Human carriers Human infections: Scarlet fever. Puerperal sepsis. Erysipelas. Septic sore throat. Pneumonia, etc.	Cattle: mastitis. Laboratory animals.	
B . .	Cattle: mastitis. Milk.		Human throat and vagina.
C . .	Horses: strangles. endometritis. Cattle: mastitis. Guinea pigs: adenitis. Also in infections of many other animals, as rabbits, foxes, swine, fowls.		Human throat and vagina.
D . .	Cheese.		Human throat, intestine and vagina.
E . .	Milk.		
F . .	Man: respiratory tract.		
G . .	Man: respiratory tract. Monkey: normal throat. pneumonia. Dog: otitis.		

Group A comprises most hemolytic streptococci which have been isolated from human infections and also includes a large number of strains isolated from human carriers. Representatives of this group have occasionally been isolated from infections in lower animals.

The most notable instance of this finding is in bovine mastitis, occurring secondarily to an infection of the milker or other attendant; and this type of mastitis has been the source, at times, of milk-borne epidemics of septic sore throat or of scarlet fever. Small animals in the laboratory have occasionally been found to be infected with Group A streptococci. Many of these animals, on the other hand, are susceptible to inoculation with Group A strains, when they are introduced parenterally.

The large majority of disease-inducing strains in domestic and wild animals have, on the other hand, been found to belong to Groups B and C; and these, in turn, appear to have little spontaneous pathogenicity for human beings, even though they be harbored in the throat, intestine or vagina. Mastitis in cattle, while most commonly induced by members of Group B or C,^{2,3} may, as above noted, be caused by members of Group A. Groups D and E, found in dairy products, and hence probably coming from cattle, have not been shown to have pathogenicity for any animal. Thus, while any of these five groups may occur in milk or dairy products, only members of Group A have any marked potential pathogenicity for man. When, therefore, members of this group are found in milk the inference to be drawn is either that the cows furnishing the milk have mastitis due to a Group A streptococcus, or that the milk has become contaminated from a sick man or from a human carrier. It seems probable, therefore, that any milk in which Group A hemolytic streptococci are found is unfit for human consumption unless pasteurized. Probably the presence of strains other than Group A in the throat, intestine or vagina of human beings arises from the consumption of milk or other food products containing them.

More detailed discussion of the specific disease-inducing capacities of Group B and C strains for lower animals would lead us too far afield; but we can state that most epidemics of streptococcal diseases among domestic and laboratory animals are caused by these groups. Possibly the disappointing results—insofar as obtaining exact parallelism between human diseases and infections in artificially inoculated lower animals is concerned—are due to the differing susceptibility of different mammalian species to different groups of streptococci. Somewhat comparable conditions exist in the case of tubercle bacilli: bovine and avian strains have much different disease-inducing capacities for man than for cattle or birds. It is to be hoped that some laboratory animal may eventually be found which will lend itself to study of Group A streptococcal infections in much the same manner as guinea pigs inoculated with human tubercle bacilli have tuberculosis comparable to that of man.

The pathogenicity of Groups F and G is little understood; but at present Long and Bliss⁴ are actively investigating this question in respect of Group F.

An excellent example of the application of the method of grouping is to be found in the recent work of Lancefield and Hare⁵ on the serologic differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women. It was found that all strains causing puerperal infections were members of Group A, while of 96 strains isolated from patients with afebrile puerpera, only 1 belonged to Group A; the others were distributed through Groups B to G. Because most severe postpartum sepsis is the result of infection with streptococci from sources extraneous to the patient,⁶ such as carriers, or from other patients with streptococcal infections, the method of grouping offers a technique for keeping these potential sources of danger from the patient at this very vulnerable period. Group A strains in the respiratory tract of the expectant mother may become very dangerous when transferred to her genital tract. Other groups of streptococci may, on the other hand, be carried by either mother or contacts with relative impunity. For this reason one of the points of attack in preventing puerperal sepsis would appear to be the immunological identification of streptococci in these individuals, and rigid exclusion of the carriers of Group A strains.

TABLE 2.—CURRENTLY IDENTIFIED SEROLOGIC TYPES OF HEMOLYTIC STREPTOCOCCI.

Group differentiation.	Group.	Type differentiation.
Differentiated into groups by specificity of carbohydrate "C"	A	Divided into serologic types on the basis of specificity of "M" substance (Lancefield ⁸), or by slide agglutination (Griffith ¹⁰).
	B	Divided into 4 or more types on the basis of specificity of polysaccharid "S" (Stableforth ³), (Lancefield ¹⁷).
	C	(Tentatively divided into 4 types on the basis of fermentation reactions) (Edwards ²); serologic types not determined.
	D E F G	Serologic types known to exist but differentiation still incomplete.

Other groups known to exist but as yet incompletely studied.

Grouping, however, is only the first step in the complete system of classification. The second requirement, particularly important for epidemiological studies, is the differentiation of types within each group. Dochez, Avery and Lancefield⁷ originally observed that strains of hemolytic streptococci associated with infections in man lend themselves to typing in much the same way as do the

pneumococci. Although this finding and corroborative observations by many workers appeared before the development of knowledge of the groups, this fact now serves as the necessary complement to the complete system classification.

The current conception of hemolytic streptococcal *typing* is summarized in Table 2. The division into groups has already been described. For type differentiation in Group A, Lancefield⁸ employs the precipitin test with acid extracts of the streptococci—the so-called M fraction—and suitably prepared immune rabbit sera. The results of this method have been shown to parallel those obtained with the specific agglutination and protection tests.^{8,9} Griffith¹⁰ advocates a special slide-agglutination technique with especially absorbed sera, and has described more than 20 types. Neither of these methods of typing is as yet sufficiently simple to permit of use by workers other than those skilled in immunologic technique.

It is unnecessary in the present paper to discuss in detail the problem of typing in the other groups of streptococci, although the principle of typing has distinct application in epidemics among lower animals.^{2,3}

Two examples of the epidemiologic application of the system of grouping and typing of hemolytic streptococci may be cited. During March, 1933, 4 cases of streptococcal otitis media occurred among measles patients in an isolation ward made up of separate rooms. A nurse in contact with these patients also developed otitis media followed by mastoiditis. A kitchen helper on the ward developed streptococcal pharyngitis. During the next month there occurred among the patients on this ward 4 additional cases of otitis media, 2 of pharyngitis, and 1 child developed cervical abscess. All of these infections were associated with hemolytic streptococci. At various times during this period 3 nurses and 1 physician, not on duty on this ward, suffered from tonsillitis.

Strains of *Strep. hemolyticus* recovered from this series of cases all proved to be members of Group A, but there was a considerable diversity of types. Two of the patients with otitis media, together with the nurse and the kitchen helper had been infected with one type, 3 of the patients with another type, 2 with a third. The remaining strains did not fall into any of the types for which differential sera were available. These studies made it evident that there had been at least four sources of infection.

During the past winter it was possible to study another institutional outbreak of streptococcus infections. This occurred in a ward made up of patients, mostly of children, suffering from nephrosis and nephritis. Within a period of 1 month, 7 of these patients suffered acute upper respiratory infections, with marked fever and signs of intoxication. Only 1 patient on the ward escaped infection. At the time of this outbreak 44 possible contacts among the hospital

personnel were shown not to be carrying hemolytic streptococci in their throats. At the same time, however, Nurse Fe., from another ward, was found to have a hemolytic streptococcal angina, and Nurse Ca., who was on duty on the ward involved, was found to be suffering from ethmoiditis of 3 weeks' duration. Swabbings from her nasal cavity at this time yielded almost pure cultures of *Strep. haemolyticus*. Obviously, both nurses were possible sources of the

	Nov.	Dec.	10	15	16	17	19	20	21	24	27	30	Jan.	3	10	13	20	27	Feb.	3	13	Mar	Ap
Pt. Ga. V	24 th F	F	A			—																	
" Re "	F & A	+				—																	
" Fa "				F		—																	
" Mo "					F																		
" Me "	—																						
" Pa "																							
" Br "																							
" Ch "																							
Nu Mc "																							
" Co "																							
Or La "																							
Nu Ca "																							
Nu Fe IV																							
Or Ha III																							
Cl. O'R Ad																							
Dr. Bo---																							
Ma DuDrD																							
" MoNuD																							
Nu PuD & K																							
" Da All																							
42 other contacts All negative																							

FIG. 1.—Summary of a hemolytic streptococcal epidemic in a ward and of other streptococcal infections among contacts. *F* indicates fever; *A*, angina; *Ol.M.*, otitis media; *My*, myringotomy; *CA*, cervical adenitis; *OP*, cervical abscess incised. Solid squares indicate that the strain of streptococcus was identified. Dotted squares indicate that the strain of streptococcus was not identified, but was probably of the type designated. Numbers in squares indicate serologic type. *U* in squares indicate types not determined. — indicates cultures showed no hemolytic streptococci. +? indicates that hemolytic streptococci were recovered but not identified. Roman numerals indicate ward where patient was ill, or where nurses (Nu) or orderlies (Or) were on duty. Ma indicates maid in doctors' dining room (Dr. D), or nurses' dining room (Nu.D). Dt.K indicates diet kitchen. Ad indicates admission desk.

ward infection. Another possible source was a clerk, O'R., who was stationed at the office desk and who handled packages and mail that were sent to the ward. Simultaneously with the ward epidemic he developed a hemolytic streptococcal pharyngitis followed by hemorrhagic nephritis.

About 2 weeks after the original outbreak 2 nurses and an orderly on duty on this ward developed severe tonsillitis. As usual, during the winter months other members of the hospital personnel devel-

oped, within this general period, angina or tonsillitis from which hemolytic streptococci were recovered.

The strains of hemolytic streptococci isolated from these patients and contacts were subjected to the various tests for classification. The results of these studies, together with the information given above, but in a highly condensed form, are presented in Fig. 1. The numerals in the various squares indicate the respective types: "U" indicates that the strain isolated did not fall into any type for which serum was available. It should be pointed out that these type numbers have no relation to those employed by Griffith,¹⁰ but are used in this particular study merely as a convenient means of designation.

From the data presented in Figure 1 it will be noted that the strains of hemolytic streptococci isolated from the patients involved in the epidemic were all of the same type. Likewise this type occurred with those three contact attendants who subsequently developed infections. On the other hand, strains from 9 other individuals, all possible contacts, either as sources of the original infection or as secondary cases, proved to be of entirely different types.

February 13, 3 of the patients had mild upper respiratory infections, and yielded cultures of hemolytic streptococci of entirely different colonial morphology from those previously observed. Further serologic study of these strains showed that they belonged to none of the groups for which sera were available. Their detection is indicated in the chart by a triangle.

From these studies it seems probable that none of the hospital personnel could have been the source of the strain which initiated the epidemic. It seems most likely that this was introduced into the ward by patient Re., who on admission was convalescing from an upper respiratory infection. Another possible source was from ward visitors, since it is well recognized that these persons often bring in infectious agents.

Discussion. As a result of the work cited, it is obvious that hemolytic streptococci can be differentiated into a system of groups and types. It has been demonstrated that the types are as highly specific as are the types of pneumococci and, like these latter, are characterized by immunologically specific chemical components. A serologic system of classification offers a basis for the elimination of much of the confusion which has obscured the problem of hemolytic streptococcal infection. For instance, in England, Griffith¹⁰ has worked for the last decade upon the question of typing hemolytic streptococci obtained from man by means of a slide-agglutination technique with broth cultures and specifically absorbed immune rabbit serum, and has found that most of the strains isolated in that country fall into 24 types. Four additional types described by him have subsequently been shown to belong in other groups of Lancefield's classification. The pathogenicity of these 4 types for

man had been questioned by Griffith; but their description among the strains commonly pathogenic for man illustrates the desirability of grouping streptococci before attempting to type them.

In collaboration with health and school officials, Griffith has been able to trace the course of many epidemics, and has shown that in institutions a primary epidemic wave was often due to one immunological type of streptococcus which, in turn, was followed by secondary waves due to the same type. In subsequent years other epidemics in the same institution were usually due to still other types. In some milk-borne epidemics Griffith found all of the patients were infected by a single type.

Some question has been raised as to whether the agglutination method employed by Griffith and the anti-M precipitin method devised by Lancefield will give absolutely parallel results in all of the types. Although this question cannot be definitely resolved until the two methods have been compared with all obtainable types, nevertheless where comparative tests have been applied with the same strains in this laboratory the two methods appear generally to agree.

Efforts have been instituted to achieve uniformity in designating groups and types in England and this country. If this most desirable goal can be attained, the methods of classification now available would permit of studies of epidemics on a much wider scale than has hitherto been possible. Sufficiently numerous data, gathered with a common viewpoint and with a uniform nomenclature, would eventually render it possible to compare other features of streptococcal infections with the types of microorganisms causing them. For example, Griffith¹⁰ has found at least 15 different serologic types in cultures from patients with scarlet fever; and Williams,¹¹ Coburn and Pauli,¹² and others have demonstrated a similar diversity of types among the strains isolated from other so-called specific infections.

We do not desire to leave the impression that all of the problems of hemolytic streptococcal infections are to be solved simply with the technique of immunologic classification, for this is probably far from the case. Streptococci have many potentialities besides the elaboration of group and type specific antigens. Erythrogenic toxins,¹³ hemolysins,¹⁴ fibrinolysins,¹⁵ leukocidins and other toxins, such as those described by Weld,¹⁶ have been demonstrated in the media of cultures grown *in vitro*, and corresponding antibodies have been found in the sera of animals and men infected with streptococci. Under suitable conditions pyrogenic functions are well marked. Certain types may have higher invasive properties than others, and hence have more marked potentialities for setting up epidemics. The same serologic type, moreover, may vary in its pathogenic capacities.

While many of the functions of streptococci are still undetermined, it is possible for clinicians and health officers to obtain a much better

understanding of some of the problems of hemolytic streptococcal infection by employing the techniques now at their disposal. The application of certain of them to epidemiologic studies have been illustrated in the examples presented in this communication; although, in view of the possibilities offered, these examples must be regarded as preliminary in nature.

Summary. Recently devised immunologic methods for classifying hemolytic streptococci into groups and types are reviewed; and illustrations are presented showing how the two categories are applicable to different situations. Grouping permits one to obtain an approximate idea of the animal species from which the strain originally arose, and of its potential pathogenicity for man. The group of hemolytic streptococci characteristically pathogenic for man (Group A) can be subdivided into serologic types; and from this typing the course of epidemics in limited populations can be accurately followed.

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ACUTE VASOSPASTIC HYPERTENSION.

A CASE WITH SIGNS OF CEREBRAL IRRITATION AND SEVERE
RETINITIS WITH REMISSION.

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Two years ago a young woman who had been under observation at the clinic for many years, became afflicted within a few months by a severe form of diffuse arterial disease with hypertension. During the early acute phase of the condition her symptoms were severe headache, transient blindness, and hemianopsia. With the subsidence of these early visual disturbances there gradually developed a diffuse retinitis which in a few weeks became so extensive that there was edema of the optic discs and involvement of the macular regions. Vision was again impaired, and the woman was unable to read. After treatment in hospital, extending over a period of 1 month, her headaches became less severe and the retinitis began to subside. Slow recovery took place in the next 3 to 4 months. For 1 year there has been no active retinitis. During this last year, in spite of continued hypertension, the patient has been able to carry out about half of her household duties, and has been free from uncomfortable symptoms except for an occasional headache and tiring easily.

Case Report. The patient, a woman, now aged 31, first came to the clinic at the age of 11 and has thus been under our observation for 20 years. On her first admission she was in good health; the complaints were minor. In August, 1920, at the age of 17, she was found to have enlarged cervical nodes, presumably tuberculous. In 1921 infected tonsils were removed; examination of the urine gave negative results. She gave, for the first time, a history of migrainous headaches, which have persisted in varying intensity ever since. In 1922 she underwent a bilateral radical surgical operation for the suspected tuberculous glands, and histologic examination confirmed the diagnosis of tuberculous adenitis. In 1924 she had her first baby. Apparently there were no untoward events during pregnancy. In 1927 vision in her left eye became poor. In 1929 she had her second pregnancy, and apparently was in normal health. During the prenatal period she had very good care and was seen by Dr. Randall and Dr. Mussey. Delivery was in July, 1929. It is interesting to note that preceding and following the delivery the patient had no albuminuria or hypertension. In October, 1929, the ocular fundi were normal except for the presence of healed tuberculous chorioretinitis in the left macular region. In February, 1930, routine urinalysis gave results which were negative, as they always had been on previous visits. In March, 1932, the blood pressure was 110 mm. Hg systolic and 70 diastolic. Previous

to that date the records of blood pressure were also within the limits of normal. In August, 1932, she came in for refraction because of headaches. No lesion was found in the fundus except the old, central choroiditis of the left eye.

In November, 1932, because of increasing severity of headaches, she came for general physical examination. The systolic blood pressure was found to be 220 and the diastolic, 140. November 29, the arterioles of the fundi were markedly attenuated, especially the nasal branches in each eye, but there was no retinitis. She was put in the hospital for observation and remained there for 1 week. The patient appeared to be healthy. She did not appear anemic, and blood examination revealed normal hemoglobin and erythrocyte figures. Her blood pressure, which was 200 mm. Hg, systolic and 130 diastolic, fell to 160 systolic and 90 diastolic. There was no demonstrable cardiac enlargement; the aortic second sound was moderately accentuated. The peripheral arteries on palpation were not definitely thickened, but gave to the examiner the sensation of a thickened rubber tube. The headache was the distressing symptom, together with attacks of vomiting. There was albumin, Grade 3, in the urine, but no red blood cells or casts. The values for blood urea and serum sulphate were normal, although urea clearance was reduced to 25 cc. of blood cleared per minute. Excretion of water was normal. While the woman was in hospital, one small hemorrhagic area appeared in the right retina (Table 1).

Two weeks later she was brought into the hospital in a stuporous, semi-conscious, peculiar mental state. She complained that her vision had become suddenly blurred following several days of severe headache. At 7.30 A.M. she was apparently totally blind; at 9.30 A.M. she was able to perceive moving objects and had a left homonymous hemianopsia.

On *physical examination* gross abnormalities were not found. The blood pressure was 205 mm. systolic and 140 diastolic. Ophthalmoscopic examination revealed marked constriction of the retinal arteries, with considerable spastic irregularity. Several hemorrhagic areas and cotton wool patches were present in the right retina. Dr. Woltman thought the woman might have tuberculous meningitis. On lumbar puncture, the cerebrospinal fluid was under a pressure of 25 cm. of water, but the fluid was normal. Removal of 12 cc. of fluid did not relieve the headache. The next day, the visual fields were normal and the woman was able to read a newspaper. There was no actual paralysis. In the course of this visit, we gave her hypertonic solutions intravenously, with apparent benefit. These solutions included 20 to 25% solution of sucrose, either alone or combined with 3% solution of acacia. However, the retinal lesions increased during her stay in the hospital. Routine urinalysis disclosed albumin, Grade 1 to 3, but no erythrocytes or casts. Studies of renal function indicated a normal concentration of blood urea, slightly elevated serum sulphate, and reduced urea clearance (46 cc. of blood cleared per minute). A fortnight after the woman's dismissal from hospital her headaches still continued, so she reentered the hospital and remained there for 4 weeks. During the 2 weeks at home her vision had failed so that she had been unable to read. Typical retinitis of so-called malignant hypertension had developed, with edema of the optic discs, numerous cotton-wool patches and hemorrhagic areas, and a partial macular star in the right eye. The arterioles were constricted to Grade 2 or 3 and the spastic irregularities were apparently developing into definite organic changes. Examination of arterioles of a small portion of the pectoralis major muscle, removed for histologic study, disclosed a decreased ratio of wall to lumen, 1.4, and a moderate increase in the intimal and medial nuclei. During this period, in January and February, 1933, we gave her repeated intravenous injections of hypertonic solutions of sucrose and glucose which also contained acacia. Deep

TABLE 1.—SUMMARY OF DATA ON THE CASE REPORTED.

Date.	Weight, kg.		Retina.			Blood.					Urine.					Comment.		
			Blood pressure.	Arterioles.	Hemorrhages, grade.	Retinitis, grade.	Hemoglobin, gm. per cent.	Erythrocytes, millions.	Urea, mg. per cent.	Serum sulphate, mg. per cent.	Creatinin mg. per cent.	Albumin, grade.	Erythrocytes, grade.	Casts, grade.	Phenolsulphonethalein, per cent.		Urea clearance, cc. of blood cleared per min.†	Sulphate clearance, cc. of blood cleared per min.
2-5-30	110	70	12.6	4.10	0	0	0	Röntgenogram of chest normal.
3-18-32	64.1	14.7	4.21	25	9	Röntgenogram of chest and head normal.
11-20-32	220	140	3	0	16	4.9	1.2	3	0	0	0	60	No intravenous therapy. Water test:
12-3-32	62.3	90	3	0	1538 cc., sp. gr. 1.002.
12-20-32	200	130	3	0	Intravenous sucrose 20 to 25%, sucrose 20% with acacia 3%;
12-20-32	205	140	3	0	4.82	22	5.7	1.3	3	0	0	spinal puncture, 1 lymphocyte, no protein pressure 25 to 2 cm. water, 12 cc. removed
12-31-32	57.3	190	3	20	3	0	0	No lead in urine. Hemiparesis. Temperature 100° F. §
1-15-33	51.5	175	3	2	22	..	1.3	3	0	0	Temperature 100° F. § Muscle biopsy, ratio 1-4, moderate increase in intimal and medial nuclei; 20% glucose and 3% acacia.
2-15-33	..	185	15.2	4.23	22	3	0	0	20% sucrose, 20% glucose with 3% acacia. Deep Roentgen therapy to pituitary.
3-20-33	53.6	215	
4-20-33	52.7	225	2	0	1	
9-9-33	56.1	240	3	0	28	
11-16-33	51.5	230	3	0	
1-11-34	51.5	210	3	0	
3-14-34	51.1	210	3	1	13.3	..	32	12	0	0	25	..	Basal metabolic rate +12.
5-11-34	53.6	210	3	0	13.3	..	27	12	0	0	Fundus photograph. Roentgenogram of thorax showed heart enlarged to Grade 1.
10-16-34†	..	215	3	0	12	0	0	T.B. cervical lymph node; Roentgen therapy. Fifteen years since first noted.
2-6-35	57.3	235	3	0	

* Residual, but not active retinitis.

† Electrocardiogram showed inverted T wave in Derivation I.

† All estimations "standard clearance."

§ Highest temperature in course of observation.

Roentgenogram of chest normal.

Roentgenogram of chest and head normal.

No intravenous therapy. Water test:

1528 cc., sp. gr. 1.002.

Intravenous sucrose 20 to 25%, sucrose 20% with acaia 3%, spinal puncture, 1 lymphocyte, no protein pressure 25 to 2 cm. water, 12 cc. removed.

No tend in urine. Hemiparesis.

Temperature 100° F. § Musclic biopsy, ratio 1-1, moderate increase in infimal and medial nuclei; 20% glucose and 3% acaia.

20% sucrose, 20% glucose with 3% acaia. Deep Roentgen therapy to pituitary.

Basal metabolic rate +12.

Fundus photograph. Roentgenogram of thorax showed heart enlarged to Grade 1.

T.B. cervical lymph node; Roentgen therapy. Fifteen years since first noted.

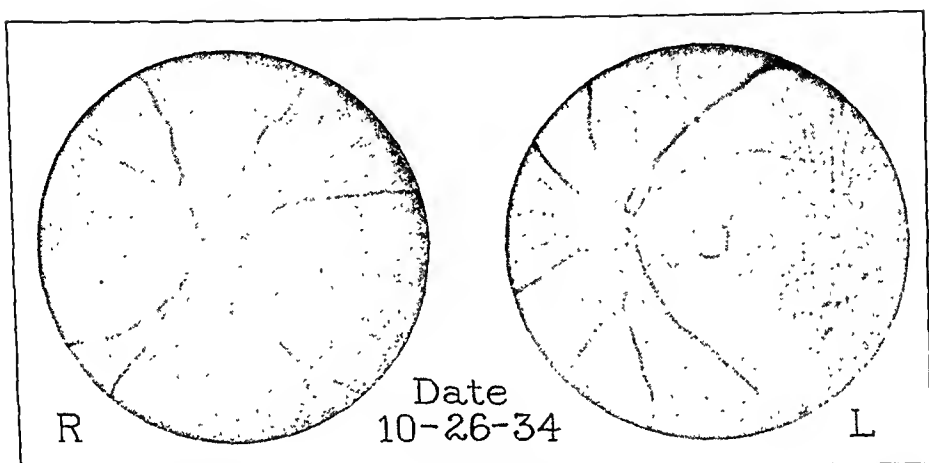


FIG. 1.—Photograph of the retina of each eye. Residual phase of acute angio-spastic retinitis. Note marked narrowing and irregularity of retinal arterioles. Healed tuberculous chorioretinitis in left macula. The condition was the same in February, 1935.

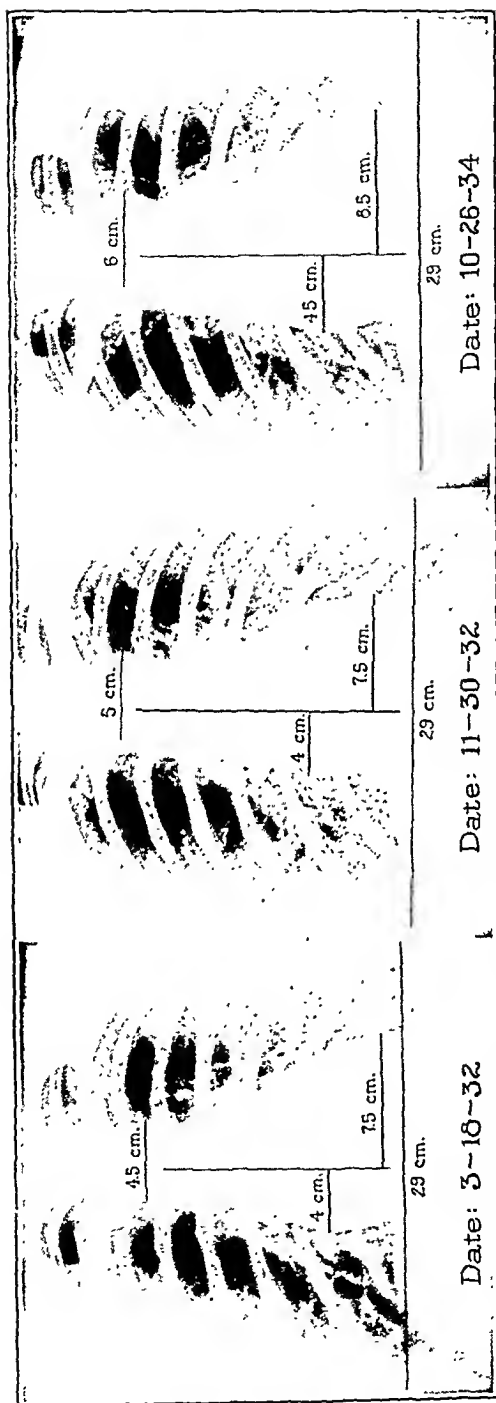


FIG. 2.—Teleoroentgenograms of the thorax. Taken as part of the routine of examination, before, at, and 2 years after, the onset of acute vasospastic hypertension. The shadow of the heart in the first photograph is of normal size; there is slight, but definite, enlargement in the third photograph.

roentgenologic treatment was administered over the pituitary gland. The woman slowly began to improve, and within a month the retinitis began to subside. The next summer she was feeling very much better.

In September, 1933, vision of the right eye was 6/7 and ability to read Jaeger 0.50. The right optic disc was slightly pale, and in both discs connective tissue was increased. The arterioles were narrowed to Grade 3, with generalized delicate perivascular sheathing, and sclerosis Grade 3. Exudate, residual from the edema, was present in the macular regions, but there were no hemorrhagic areas or cotton-wool patches.

In October, 1934, the original difficulties had not all cleared up. There were still slight residual signs of the retinitis, but it had now been more than a year since the retinitis had been active. The arterioles of the retina were still narrowed (Grade 3) and sclerosed (Grade 3), as may be seen in Figure 1. The condition had not changed at the last examination, February, 1935. The woman seemed to be in very good condition and felt well. Her weight was normal. She recognized that she was easily fatigued, but if she restricted her activities moderately, this was controlled. She slept well, and her headaches were much less frequent and not so severe as they had been. Her blood pressure on October 16 was 215 mm. systolic and 145 diastolic. There was slight but definite increase in the size of the heart (Fig. 2); the aortic second sound was accentuated to Grade 2, but murmurs could not be heard. The peripheral arteries still felt rubbery, but no more so than they had felt 2 years previously. There was albumin, Grade 2, in the urine. The value for blood urea was normal, but the urea clearance was reduced to 25 cc. of blood cleared per minute. On an electrocardiogram, the *T* wave in derivation 1 was inverted.

The patient returned to the clinic in February, 1935, because of a small lump which had become noticeable in the right parotid region. This was diagnosed as a recurrence of the previous tuberculous adenitis, and Roentgen therapy was instituted. Thus, for 15 years, the patient had had tuberculous cervical adenitis. The condition of the retinae at this time was unchanged, and was still unchanged April 30, 1935.

Discussion. The rapid onset of retinitis, without preceding arteriosclerosis, in a case of hypertensive disease of this type, is interesting and rather difficult to explain, unless it is assumed that there is present a very acute angiospastic process similar to that seen in hypertensive toxemia of pregnancy, with resultant ischemia and anoxemia of the retina.⁶ Occasionally retinitis is seen in a case of acute nephritis, but the retinitis is usually mild and transitory unless the disease goes on rapidly to the chronic stage. The retinitis in the case here reported was diffuse and severe. At the time of the onset of the retinitis, this patient had an attack suggesting cerebral angiospasm. There was, in addition to stupor and mental confusion, rather sudden, complete loss of vision of both eyes. In a few hours vision returned in the right halves of the visual fields, and in about 12 hours the fields were normal. We assumed that the loss of vision was cerebral, associated with cerebral angiospasm, and that vision returned when the spasm passed. However, it is of interest that there is a history of previous, and subsequent, attacks of migraine with hemianopsia. The striking feature in the retina, in the course of the present illness, was very marked, generalized narrowing and spastic irregularity of the retinal arterioles. The retinitis rapidly

increased in severity and diffuseness until there was a typical, so-called "albuminuric retinitis," with definite edema of the discs and generalized edema of the retina, in which macular stars gradually developed. In most cases of this type retinitis does not show a tendency to resolve,⁴ whereas in this patient's case there was, after the first 6 weeks or 2 months, a very definite tendency to resolution of the retinitis. Almost 2 years after the onset, from the standpoint of retinitis proper, there was very little residual trouble. There had not been any appearance, recently, of fresh hemorrhagic areas, cotton-wool patches, or return of the edema of the retina.

Such subsidence of severe retinitis was noted by Liebreich,¹ who first described the ophthalmoscopic findings of albuminuric retinitis in 1859. Fishberg and Oppenheimer,² in 1930, reported in a case of malignant hypertension the healing of severe retinitis with no recurrence over a period of 4½ years. The writers reported a similar case in 1929³ and since that date have seen 4 additional cases.

It is well recognized that retinitis does not often recur in a second attack of toxemia of pregnancy. This may be because the arteriolar walls have in some way lost their capacity for active narrowing and dilatation. The cessation of sudden variations in caliber, and their consequent interference with the circulation of the retina, may account for the gradual healing of the retinitis. The coincidence of subsidence of the retinitis with definite improvement in the general physical condition suggests, however, that the active angiospastic factor which was apparently the initial cause of the retinitis, and of the rise in blood pressure, is less active or relatively dormant.

There has been no recurrence of the acute cerebral symptoms in the last 2 years. It is difficult to ascribe such severe cerebral symptoms, and the accompanying increase in cerebrospinal fluid pressure, to an attack of migraine. The headaches have been much less severe and less frequent than before. Complaint of vertigo has not been made. Hypertension has persisted since the onset, but palpation of the peripheral arteries does not indicate distinct thickening of their walls. There never have been any clinical signs of myocardial decompensation, although last October there was evidence of myocardial injury, as indicated by inversion of the T wave of the electrocardiogram. Abnormal urinary findings and renal functional disturbances have persisted, as has the hypertension, since the onset. The absence of erythrocytes, even on microscopic examination, in many routine urine analyses, is noteworthy. Renal disturbances never have resulted in serious demonstrable renal insufficiency or in characteristic symptoms of renal impairment. Secondary anemia has not developed in 2 years of illness. Clinicians have observed, and have stated, that patients who have chronic tuberculous lesions rarely have increased blood pressure. In the present case, tuberculosis of the lymph nodes in both cervical chains was present many years before the onset of hyper-

tensive disease, and is still present. It is difficult to establish any definite relationship between these two conditions in the present case.

Naturally the question arises as to whether the rather intensive use of hypertonic solutions intravenously, and of Roentgen therapy, was related to the relatively rapid subsidence of serious symptoms, and the diffuse retinitis. We believe that these measures were possibly beneficial, but lack of control renders it impossible to make a categorical statement. At least, it can be said that harmful effects from these forms of treatment have not been noted.

In spite of the rather favorable course in this case thus far, we feel that the ultimate prognosis must be guarded. From the general clinical and retinal findings, we should be tempted to place such a case as this in Group 2⁵ type of diffuse arterial disease with hypertension, if we performed examination for the first time in the stage of remission. This patient has adequate cardiac and renal function. She does not have edema of the discs or active retinitis. It would be difficult to say that edema of the discs ever had been present. In a few months more it probably will be difficult to determine whether this patient ever had retinitis. However, with the evidence of previous cerebral irritation and retinitis, she should be considered in the Group 3 type of diffuse arterial disease with hypertension. Further observation of this, and other similar cases, is the only method available at present for determining the ultimate prognosis.

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A SUGGESTION FOR SIMPLE TREATMENT OF ACUTE ARTERIAL SPASM.

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THE part played by vasospasm of collateral channels in the ischemia of a region following acute occlusion of its major artery is receiving increasing recognition. This recognition has opened new

possibilities for the conservation of tissue. The present contribution suggests a simple method of treatment directed towards the release of such collateral vasospasm.

The effect of sympathectomy on collateral circulation after arterial occlusion has been studied in the laboratory.¹ Nystrom³ is in agreement with the conclusions expressed by Gosset, Bertrand and Patel,⁴ Denk⁵ and Allen and MacLean² on the important influence of spasm in this condition. Gage⁶ has abolished the sympathetic impulses by alcohol injection of the lumbar ganglia before ligating the common iliac artery for aneurysm, and Bird⁷ has performed lumbar sympathetic ganglionectomy before operation for popliteal aneurysm. Lehman,⁸ following the suggestion of Leriche,⁹ has carried out arteriectomy when ligation is necessary, believing that a perivascular sympathectomy is thereby effected. Allen and MacLean,² following the suggestion of Denk,⁵ employed papaverin as an antispasmodic to tide a patient suffering from arterial embolism over the period of active vasospasm.

Sympathectomy either by excision or by alcohol injection is, of course, the most direct and sure method of preventing vasospasm in a part. It is probable, however, that the vasospasm following sudden arterial occlusion or the mechanical stimulation of the arterial wall is transient, and such measures are therefore too radical. As is well known, the vasospasm that follows such extensive local stimulation of a bloodvessel as that incident to periarterial sympathectomy lasts only about 16 hours. Temporary vasodilatation with papaverin was apparently successful in one leg in Allen and MacLean's case. It would seem that in addition to passive vascular exercises,¹⁰ any of the expedients employed for temporary vasoconstrictor release for diagnostic purposes could theoretically be employed for therapeutic purposes. The choice of method for simplicity, applicability and effectiveness must be determined by repeated clinical trial.

Coller and Maddock¹¹ showed that complete peripheral vasodilatation can be obtained even in the presence of vasospastic conditions by creating a physiologic demand for heat loss. This they accomplished by raising the general environmental temperature through the simple method of applying blankets to the body and thus preventing radiation. They proposed this method as a means of measuring the vasoconstrictor element in arterial disease accompanied by diminished volume flow of blood to a part. The adaptation of this simple diagnostic procedure to the therapy of possible vasospasm accompanying an arterial lesion was employed in the following case.

Case Report. W. M. (No. 115991), white, single, aged 17, was admitted to this hospital April 2, 1935, and discharged May 17, 1935. Four years earlier he had suffered from a perforating wound of the left thigh caused by a .22 caliber bullet and resulting in a traumatic aneurysm just proximal

to the passage of the femoral artery through the adductor magnus tendon. Occasional pain had been the only striking symptom until 4 days before admission when an acute syndrome had supervened, consisting of pallor changing to cyanosis, cramps in the calf, swelling of the foot and ankle, and pain in the region of the aneurysm. Examination on admission showed coolness and marked cyanosis of the left foot with darker reddish patches scattered over the lower leg and toes. The color changes were increased by the dependent position. There was a slight pitting edema. The left calf measured 35 cm. in circumference, the right 33.5 cm. The posterior tibial and dorsalis pedis arteries were easily identified on the left, although the pulsations were somewhat less strong than those of the corresponding vessels on the right. There was no dilatation of superficial veins. The aneurysm was firm, tender, and somewhat diffuse in outline; it presented only moderate expansile pulsation. Roentgen ray showed calcification of its walls. There was a soft systolic bruit. General physical and routine laboratory examinations were of no significance. There was no evidence of cardiac enlargement. The blood pressure ranged around 120 mm. Hg; the pulse pressure around 50 mm. The blood Wassermann and Kahn tests were negative.

The cause of the acute developments superimposed upon the old arterial lesion was never satisfactorily explained. Arteriovenous fistula, rupture of the false aneurysmal sac, massive embolism or thrombosis were all satisfactorily ruled out by pre-operative examination and the operative findings. The syndrome was made particularly puzzling by the fact that the reddish discolored patches on the calf, shin and toes eventuated in scaling or even extremely superficial loss of tissue, while the distal pulsations remained active.

A possible explanation presented itself during the period of observation, when it became evident that the patient suffered from marked generalized vasomotor instability. The local condition improved progressively with rest in bed and local heat applied by the heated foot cradle. Pain diminished, color improved except for the markedly changed patches, swelling disappeared and the aneurysm became less tender and more definite in outline. However, on at least one occasion the left leg again became blue. Examination at this time showed the right leg also and both hands to be blue, cool and moist. Surface temperature tests showed a difference of from 1°C. to 2.7°C. between corresponding areas of the two feet, the diseased foot being the warmer. It was therefore thought possible, as an explanation of the acute syndrome, that a small embolus, detached from the aneurysm and lodging in an artery distal to the level of ordinary vessel palpation, might have resulted in an attack of local vasospasm, exaggerated by general vasomotor instability to a degree sufficient to cause actual though slight tissue necrosis before gradual relaxation of the vessels.

This observed attack of generalized vasoconstriction further suggested the danger of such an attack following operation on the aneurysm. The vasomotor response to sympathetic paralysis was therefore tested prior to operation under spinal anesthesia, partly in order to measure the reaction that could be expected if intervention on the sympathetic function seemed to be indicated after operation on the aneurysm, and partly as a matter of clinical interest in a case presenting a local organic arterial lesion together with vasomotor instability. Normal vasodilatation levels were observed in both legs.

After 17 days of observation the aneurysm was exposed and entered under spinal anesthesia and a tourniquet. A lateral opening in the femoral artery was found, leading into a false aneurysmal sac about 4 inches in diameter, filled with old degenerated and partly organized blood clot. The wall of the sac was thick and contained much calcium. There

had been no recent rupture or bleeding into the sac itself. A typical restorative endoaneurysmorrhaphy was done with preservation of the entire sac wall. In closing the opening into the artery, the tissues were so badly scarred and calcified that only rather deep bites of the needle would prevent cutting out of the silk sutures. It was therefore feared that the lumen of the femoral artery might have been somewhat narrowed.

The patient was examined as soon as complete sensation had returned to the feet. The left foot was paler, more cyanotic and cooler than the right. Arterial pulsations were present in the right foot and ankle and absent in the left. Capillary return on the left was somewhat slow. Differential diagnosis lay between occlusion of the femoral artery by suture, and vasospasm from mechanical stimulation of the arterial wall. The leg and foot were thickly wrapped in a roll of absorbent cotton. For about an hour there was no improvement in appearance. The patient was then wrapped up to the neck in two blankets and a body cradle, warmed with electric light bulbs, was placed over him. The local improvement after this procedure was striking. Within less than an hour the foot was warm and pink and within 2 hours the pulsation of the dorsalis pedis artery could be perceived. At this time the patient noted that the foot and leg felt better than at any time since the original injury 4 years earlier. The body temperature was recorded at frequent intervals during the period of immediate postoperative observation. The highest temperature reached within the first 24 hours was 99.4° F. by mouth. The elevated environmental temperature was maintained for about 36 hours.

Convalescence was thereafter uncomplicated except for persistent blueness of both feet when the patient was first allowed to sit up. This was definitely worse in the left foot. It was overcome by postural exercises with carefully graduated activity. The wound healed *per primam*.

It has long been established surgical practice to protect an ischemic extremity from heat loss by bandages of cotton-wool and the application of external heat with hot-water bottles or with warm air from electric lights beneath a cradle. The rationale of this procedure has probably two elements. In the first place, it is hoped that the conservation of heat may delay necrosis until collateral circulation is established. In the second place a reactionary hyperemia is hoped for from local vasodilatation such as occurs when the hand is immersed in hot water.

To create a physiologic demand for heat loss by increasing the general environmental temperature is perhaps more logical in view of its proven effectiveness in vasospastic conditions¹¹ and certainly not more complicated or difficult than to wrap the involved extremity alone. In the case cited there is no proof of its effectiveness; there is, however, reason to assume its effectiveness.

The suggestion is made, therefore, that in all cases of suspected acute vasospasm the principle of Collier's diagnostic test be applied therapeutically. Collier¹² states that he does not know of any such application previously and no reference to it has been found in the literature. If further clinical experience confirms the benefits, expected *a priori* and perhaps demonstrated in this case, this method may become one, among others (such as the use of vasodilator drugs and of passive vascular exercises) to be chosen when sympathectomy is not justified.

Specifically it is suggested that all patients suffering from arterial embolism and all patients in the period immediately following operations on the arteries be exposed to increased general environmental temperature by being enveloped in blankets as a primary treatment. This procedure will serve to fix the value of the method and may easily prove of enormous benefit to individual patients.

Conclusion. 1. Vasospasm of collateral channels in acute arterial occlusion and following surgery on the arteries is being emphasized in surgical thought.

2. The control of such vasospasm by sympathectomy is certain but radical.

3. Simple methods, such as vasodilator drugs and passive vascular exercises, have been used for control of vasospasm successfully.

4. It is suggested that Collier's diagnostic test for vasospasm (elevation of the environmental temperature) may have therapeutic possibilities in this connection. A case is presented which tends to confirm the suggestion.

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A STUDY OF THE VENOUS BLOOD PRESSURE IN SOME COMMON DISEASES.

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CARDIAC failure with congestion is of frequent occurrence and easy of diagnosis. It may be recognized by the presence of breathlessness, engorgement of the veins, enlargement of the liver, cyanosis, peripheral edema, ascites and edema of the lungs. Much attention has been paid to many of these phenomena, but not to the study of the veins which frequently affords the first signs of circulatory breakdown. "Direct measurement of the venous pressure," writes Sir Thomas Lewis,¹ "will often provide an invaluable guide to the patient's state; repeated readings will often indicate clearly the course of the malady." The present paper was prepared in order to emphasize the value of measuring the venous blood pressure at the bedside. In the pages which follow, the term "congestive heart failure" will be used in the sense defined above. The criteria for diagnosis of the several heart disorders described are, in the main, set forth by Lewis¹ and will be given in more detail under the appropriate headings.

Methods. The direct method of Moritz and von Tabora, as modified by Griffith, Chamberlain and Kitchell,² was employed. The desired vein (usually the antecubital) was punctured with a needle and the saline solution filling the manometer tube was allowed to run into the vein until a stationary level was reached. The readings were obtained directly in millimeters of water (for practical purposes the specific gravity of 0.9% NaCl is the same as that of water). It may be necessary at times to correct for the capillary action of the tube, but with the particular apparatus used this correction was negligible. The determinations were made whenever possible under basal conditions, the patient lying in the dorsal position with the vein at the level of the right auricle which is at the midaxillary line. This procedure was impossible with many of the cardiacs, so that in these cases the readings were taken with the patient in the sitting position with the arm elevated to the level of the right auricle. In this manner comparable measurements were obtained. Serial determinations were made at intervals on many of the heart patients to observe the course of their disease.

Findings. The material which forms the basis of this paper consists of 366 determinations of the venous blood pressure of 215 patients. Early in the study all cases admitted to the medical wards were tested, but as the work progressed only cases of especial interest were chosen.

The results have been arranged graphically so that one may quickly grasp the important features. In the charts (Nos. 1, 2, 5, 6, 7) each venous pressure determination has been represented by

an open circle if the patient presented no clinical evidence of cardiac failure with congestion or by a closed circle if the signs of congestion were present. Repeated determinations on the same patient have been placed beneath one another in the same vertical line. If a patient died, a small cross has been placed just above the reading which was made nearest to the time of death. By observing whether the circles are closed or open and whether in the upper or lower portion of the charts, one may correlate at a glance congestive heart failure with elevation of venous pressure.

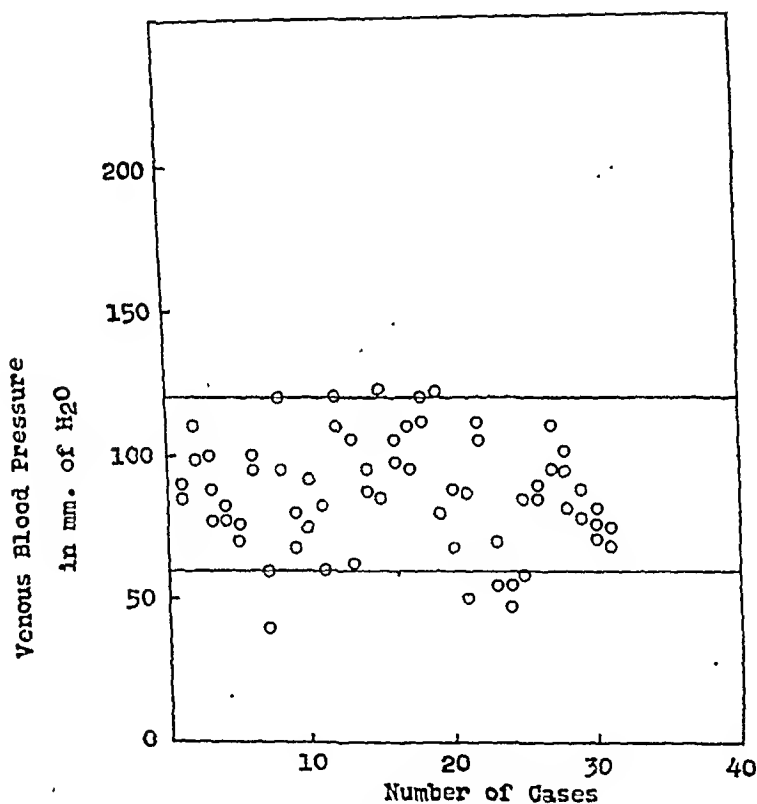


CHART 1.—The control series. Duplicate venous pressure determinations in 31 patients with a normal circulation. The area between the two parallel, horizontal lines is the zone of normal variation.

Control Series. Thirty-one patients who were known not to have presented evidences of circulatory involvement were used as a control group. Duplicate readings were made on these subjects on successive days under basal conditions. The average venous blood pressure for the control series was 83 mm. of H₂O and the mean difference of the two readings with the standard deviation of the difference was 16 ± 11 mm. of H₂O. For the purposes of this paper normal venous pressure is assumed to lie between 60 mm. and 120 mm. H₂O, which are the limits usually accepted.^{2,3}

Arteriosclerotic Heart Disease. It was found convenient to accept an etiologic classification of the diseases of the heart, which have been divided into (1) arteriosclerotic, (2) rheumatic and (3) miscellaneous diseases of the heart, including cases of syphilitic and bacterial origin.

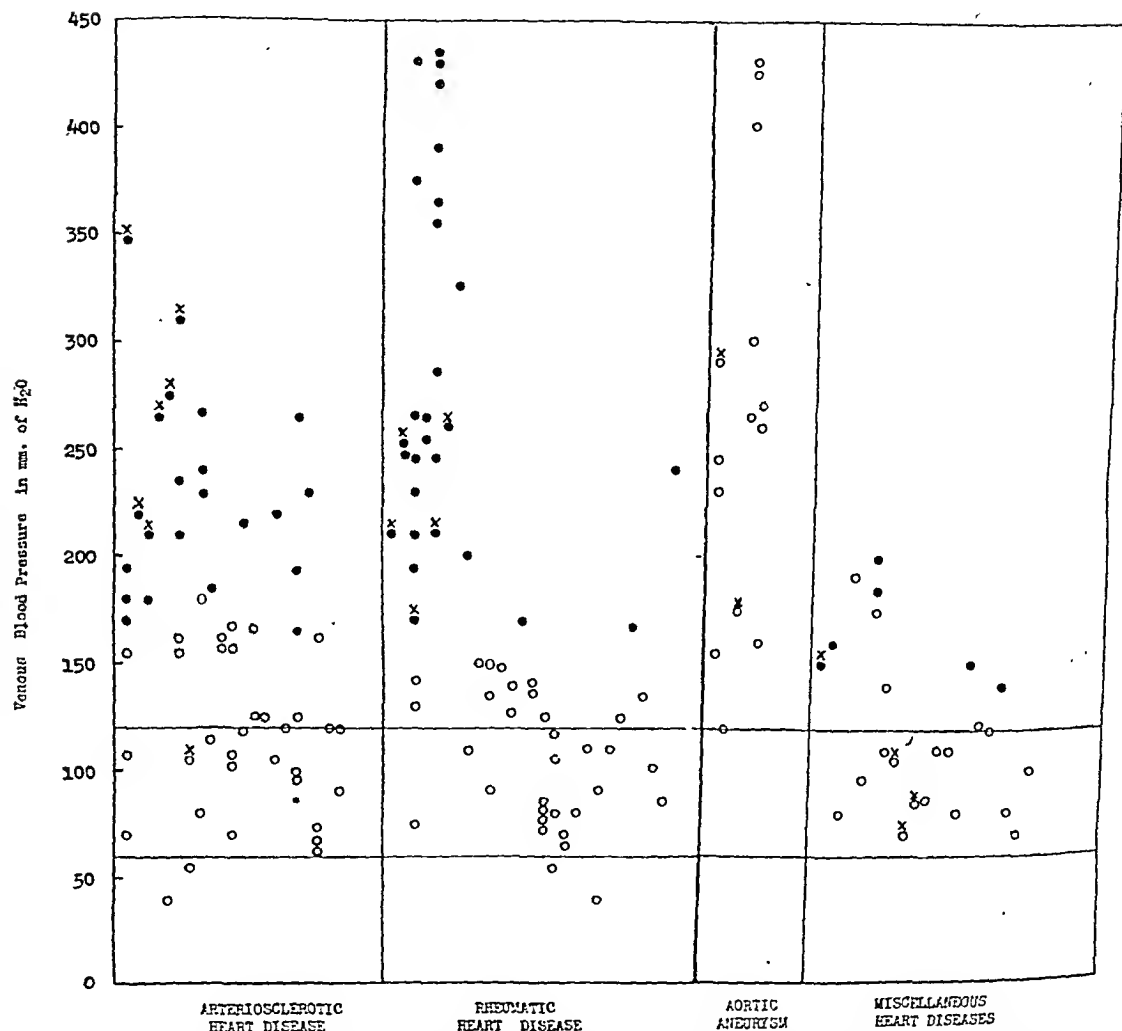


CHART 2.—Behavior of the venous blood pressure in heart disease. Cases with congestive heart failure are represented by solid circles and those without congestive failure by open circles. Serial readings are placed beneath one another in the same vertical column. A cross has been placed over the reading taken nearest to the time of death in the fatal cases. The area between the two horizontal lines is the zone of normal variation. The number of cases is plotted along the abscissa.

The arteriosclerotic group consisted of 20 cases. Many of them were cases of coronary thrombosis in which the diagnosis was made either at autopsy (4 cases) or on the presence of such typical findings as protracted anginal pain and the manifestations of collapse and

cardiac failure. Delayed signs such as fever, leukocytosis, pericardial friction rub and evidences of embolism sometimes occurred. Changes in the electrocardiogram such as plateau formation, high take-off or inversion of the *T* wave in one or more leads, and an absence of the *Q* wave in Lead IV were observed in many subjects.

Also included were some cases of essential hypertension with evidences of cardiac involvement. There were signs of hypertrophy of the heart, especially of the left side; accentuation and reduplication of the first sound at the base of the heart; gallop rhythm at the apex; and systolic murmurs at the base. There were no signs of primary inflammation of the kidneys, intracranial pressure, suparenal tumor or chronic lead poisoning. A few individuals had suffered vascular accidents of one sort or another.

Several elderly patients were encountered in whom the diagnosis of chronic arteriosclerotic heart disease ("chronic myocarditis," "senile heart," etc.) was made. They usually complained of pain over the precordium and breathlessness on exertion. Examination of these patients revealed some or all the following signs; auricular fibrillation, heart block, bundle-branch block, gallop rhythm, pulsus alternans or inversion of the *T* waves in the electrocardiographic record.

Inspection of Chart 2 shows that cardiac failure with congestion occurred frequently in arteriosclerotic heart disease and was invariably accompanied by an elevation of the venous blood pressure. Of the 20 patients studied, 8 (40%) died, while of the remainder, 11 (55%) improved sufficiently to be discharged. The behavior of the venous pressure was typical (Chart 3, Case 1). It consisted of a gradual and prolonged increase in pressure, ending in a sudden rise, due probably to terminal dilatation of the right side of the heart, death following rapidly thereafter.

A moderate elevation of venous pressure was found in some patients (150 to 200 mm. H_2O) without other signs of congestive heart failure. These cases may be followed with serial readings to great advantage as they form a class which may be called "the potentially decompensated," since they possess all the potentialities of heart failure and are indeed living beneath the sword of Damocles.

The cases which, although presenting evidences of cardiac failure with congestion on admission, improved with appropriate therapy, showed a definite decrease in the venous blood pressure until a normal level was reached. Upon the ability of the patient to maintain this normal level of venous pressure depended his future well-being (see Chart 3, Case 2).

Rheumatic Heart Disease. Heart failure with severe congestion and a high venous pressure was encountered most frequently in rheumatic carditis. The present series includes cases of chronic rheumatic heart disease as well as some examples of acute rheumatic fever with signs of early mitral stenosis. The diagnosis of rheumatic

heart disease was made only if the history indicated clearly an attack of acute rheumatic fever* during childhood or adolescence, and if the usually accepted evidences of mitral valvulitis were present. Simultaneous involvement of the aortic valve was noted in some cases. A few patients with acute rheumatic fever, but without signs of cardiac disturbance were also included for purposes of comparison.

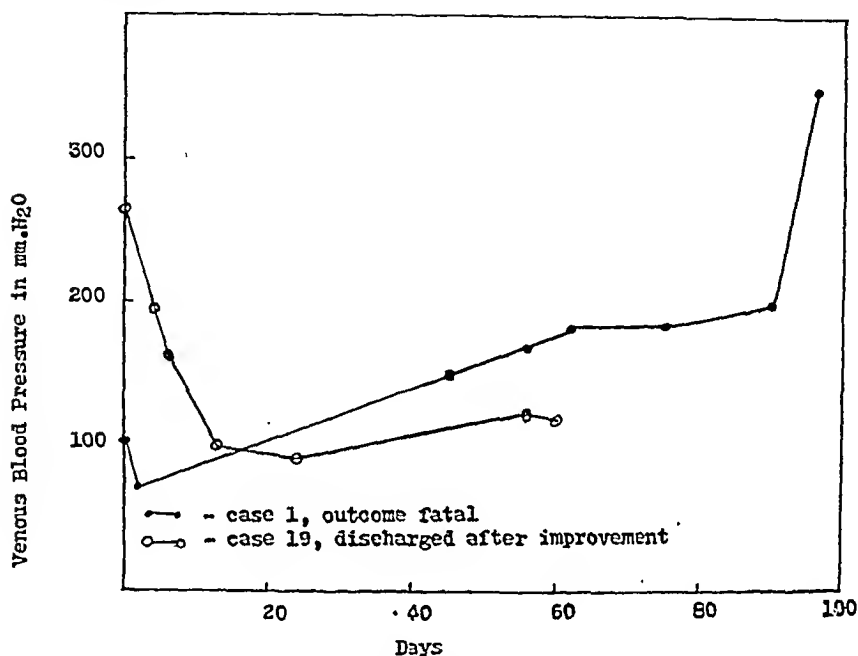


CHART 3.--The course of the venous blood pressure in 2 typical cases of arterio-sclerotic heart disease.

Of 28 patients studied, 4 (14.3%) died. The deaths occurred in those patients with a pronounced elevation of venous pressure and congestive failure of the heart. The characteristic feature of the venous pressure in these fatal cases was that it could not be reduced to a normal level and subsequently maintained there (Chart 4). The individual venous pressure readings of the rheumatic fever group have been recorded in Chart 2. It will be observed that cardiac failure with congestion often ensued when the venous pressure rose above 150 mm. H₂O. One case was of especial interest, for although the patient showed marked clinical improvement, the venous pressure did not change. On the basis of this finding a grave prognosis was given. Several days later death occurred quite suddenly.

The value of serial determinations of venous pressure in following the course of rheumatic heart disease is well illustrated in Chart 4.

* The term "rheumatic fever" is used here in the wider sense of the rheumatic state.

This patient, a woman in middle life, was admitted to the hospital suffering from congestive failure of the heart. Her condition was desperate. She was bled 500 cc. and the venous pressure which had previously been near 400 mm. H_2O immediately dropped to 240 mm. H_2O with great relief of symptoms. Improvement continued during the 3 weeks she remained in the hospital and at the time of her discharge the venous pressure was 65 mm. H_2O . Under

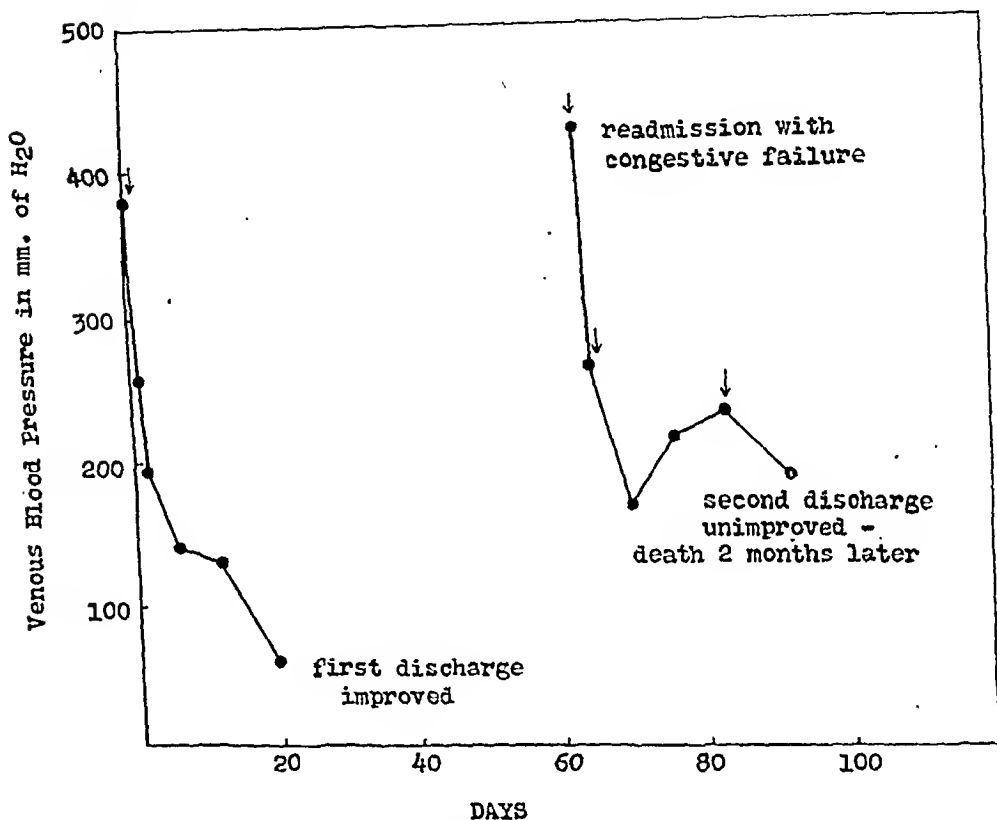


CHART 4.—Behavior of the venous blood pressure in a typical case of chronic rheumatic heart disease with mitral stenosis, auricular fibrillation, anasarca, and congestive failure. The good response to treatment on the patient's first admission is in contrast to the poor response on her readmission. The case is described in detail in the text. The arrows indicate phlebotomy.

adverse living conditions at home, circulatory failure recurred, obliging the patient to again seek hospital treatment. The venous pressure on this admission was 430 mm. H_2O ; just 6 weeks after her former discharge. Phlebotomy was performed, but without giving much relief, although the venous pressure fell nearly 150 mm. H_2O . During the course of the second admission the venous pressure remained fixed between 200 and 240 mm. H_2O . Dyspnea, cyanosis and ascites persisted notwithstanding the use of digitalis, various diuretics and the paracentesis needle. At the end of a month the patient voluntarily left the hospital; 2 months later she died.

Many victims of rheumatic fever were admitted to the wards suffering from obvious heart failure with congestion. Repeated observations of the venous pressure of these individuals afforded an accurate indication of the degree of cardiac failure and a reliable estimate of the immediate prognosis. The test was also of great value in choosing the proper cases for venesection. In the presence of congestive heart failure with a venous pressure of 200 mm. H_2O , or higher, the patient was bled 400 to 600 cc. unless a marked anemia contraindicated the procedure. If the pressure in the veins fell immediately, symptomatic relief followed promptly and the patient recovered from the attack. If, on the other hand, the venous pressure was not lowered by bleeding, then the prognosis was ominous.

Aneurysm of the Aorta and Other Mediastinal Masses. The cases with aortic aneurysm were of peculiar interest. Of 4 cases observed, 3 showed a marked elevation of venous pressure. The clinical appearance of these patients was remarkable (Chart 2). Picture to yourself a patient with a high venous pressure who does not present signs of cardiac failure, but, instead, is able to walk about the ward without great effort; who complains more of headache and throbbing of the bloodvessels than of dyspnea and edema. There is only one lesion which may cause such a syndrome: a mediastinal mass obstructing the return of blood to the right auricle. The presence of an aneurysm, as in these cases, is easily demonstrated by fluoroscopic examination and confirmed by a positive Wassermann reaction. Other mediastinal masses besides aneurysm may, of course, give rise to similar findings. Thus Case 5 was a young boy suffering from Hodgkin's disease, in whom the Roentgen ray revealed huge mediastinal masses. The venous pressure was 265 mm. and 255 mm. H_2O on two different occasions. After intensive Roentgen ray therapy the masses disappeared and the venous pressure fell to 160 mm. H_2O .

It is worthy of note in Chart 2 that although many of the cases with mediastinal masses had an excessively high venous pressure, none showed signs of congestive heart failure. In 1 of the patients with an aortic aneurysm the venous pressure was normal. This was interpreted to indicate little or no encroachment of the mass upon the superior vena cava or right auricle of the heart.

Miscellaneous Disorders of the Heart. This group includes several diverse conditions (Chart 2). There were 7 cases of syphilitic heart disease in which the diagnosis was made on the findings of a positive Wassermann reaction, signs of aortic regurgitation, and in some cases of a failing circulation. Four cases of subacute bacterial endocarditis were encountered showing positive blood cultures, embolic phenomena, continued fever, clubbed fingers, splenomegaly, and clear evidence of heart disease. Three of the patients died and the diagnosis of subacute bacterial endocarditis was verified at autopsy.

In each case death occurred from cerebral embolus. There were also a number of cases in which cardiac disease was present either with or without failure and congestion, but in which a definite etiologic diagnosis could not be made.

All these cases may be quickly dismissed after remarking that a high venous pressure was observed only in the presence of congestive heart failure (Chart 2).

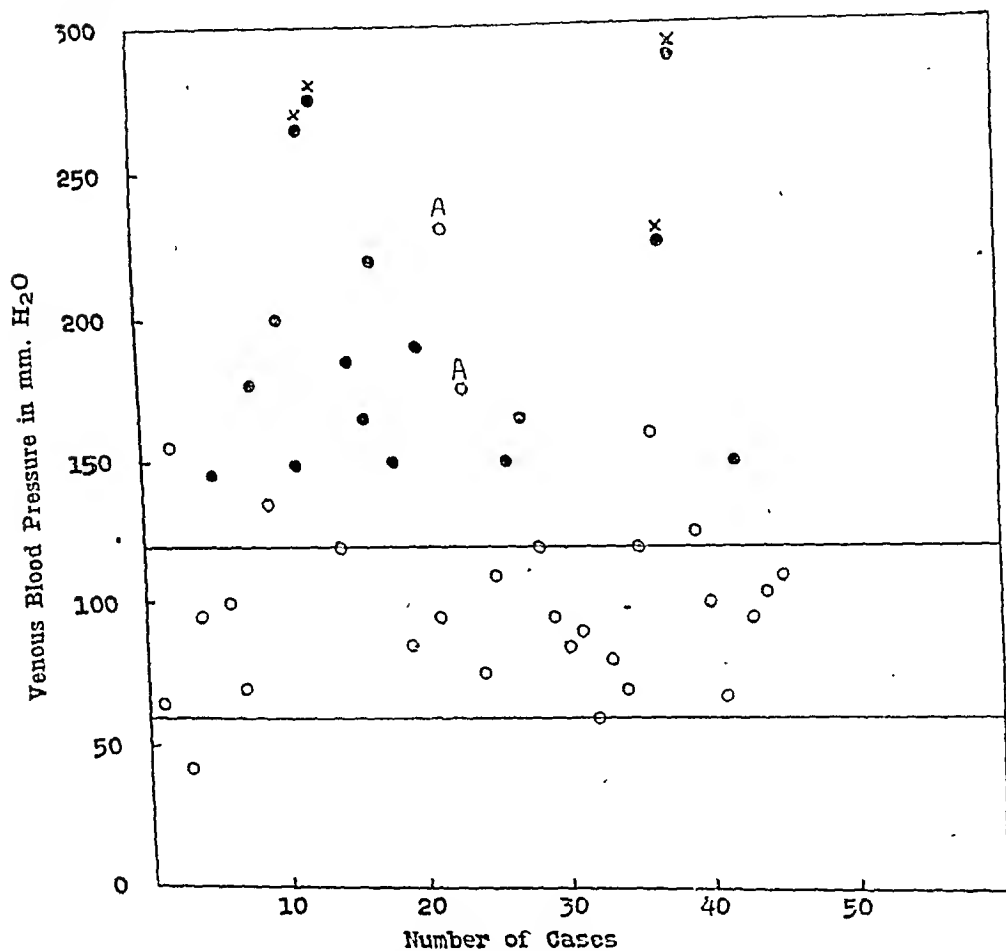


CHART 5.—Behavior of the venous blood pressure in hypertension. Symbols as in Chart 2. The letter "A" has been placed over 2 cases of aortic aneurysm, in which condition a high venous pressure may occur without signs of congestive heart failure.

Hypertension. The mutual relationship of the arterial and venous blood pressures has interested investigators since the time of the Rev. Stephen Hales (1732). In the present study 44 cases were encountered with a systolic pressure of 150 mm. Hg, and a diastolic pressure of 100 mm. Hg or higher. The average arterial pressure of these cases was 185/106 mm. Hg, and the average venous pressure

136 mm. H_2O . It will be noted that the average venous pressure was slightly above the upper normal limit. Inspection of Chart 5 explains this apparent increase of venous pressure in hypertension. It is seen that the high readings are represented by solid circles, indicating that the patients showed clinical evidences of cardiac failure with congestion. This was, of course, to be expected, for congestive heart failure is a frequent termination of many cases of hypertension. If the cases with congestion were omitted from the calculation, the average venous pressure would be 111 mm. H_2O , an entirely normal figure, whereas the arterial pressure would remain at 188/106 mm. Hg. Attention may also be drawn to the cases of rheumatic heart disease where exceedingly high venous pressures occur frequently, although the arterial pressures are uniformly low. The evidence at hand indicates that in cases of hypertension due to any cause whatsoever, an elevation of the venous blood pressure appears only with the onset of congestive failure of the heart and is probably one of the earliest signs of such an occurrence. This concept of the independence of the venous and arterial blood pressures has been accepted by many recent workers and is supported by much experimental work.⁴⁻¹⁰

Thyroid Disease. It is perhaps not amiss to mention in this place those patients suffering from thyrotoxicosis, for each of them is a case of potential heart disease. Fifteen patients were examined whose complaints were of sufficient severity to require hospitalization. The signs of toxicity consisted of an increase in the metabolic rate, nervousness, loss of weight, exophthalmos, and a thyroid mass. In some cases there were also disturbances of the circulation, such as tachycardiac, vasodilatation, auricular fibrillation, anginal pain and the usual evidences of cardiac failure.

Chart 7 shows that an increase in venous pressure was seen only in the presence of congestive cardiac failure. The venous pressure level was also of value in determining the length of the pre-operative treatment in the patients selected for operation.

Disease of the Respiratory System. The influence of disorders of the respiratory system upon venous pressure is of great interest, since their differentiation from circulatory disturbances may be difficult. Three common respiratory diseases were studied, pulmonary tuberculosis, bronchial asthma and lobar pneumonia (pneumococcus, see Chart 6). The average venous pressure for all the cases tested was 120 mm. H_2O , which is a high normal value. When a definite elevation of venous pressure occurred, as it did in 15.4% of the total cases, it was usually accompanied by some evidence of circulatory embarrassment. One of the tuberculosis patients had a marked shift of the heart to the right following pneumothorax and another showed cardiac hypertrophy. On the wards the determination of the venous pressure proved to be an easy and reliable means of differentiating between cardiac and respiratory disorders.

Miscellaneous Diseases. A large variety of diseases was studied during the course of this investigation and the venous blood pressure determinations have been recorded in Chart 7. The results are remarkable for the fact that a significant elevation of venous pressure was found only in patients suffering from congestive failure of the heart. The only exceptions to this were certain cases of mediastinal masses in which the increase in pressure has been already described. In all other cases the venous pressure was within normal limits and remained so unless cardiac failure threatened.

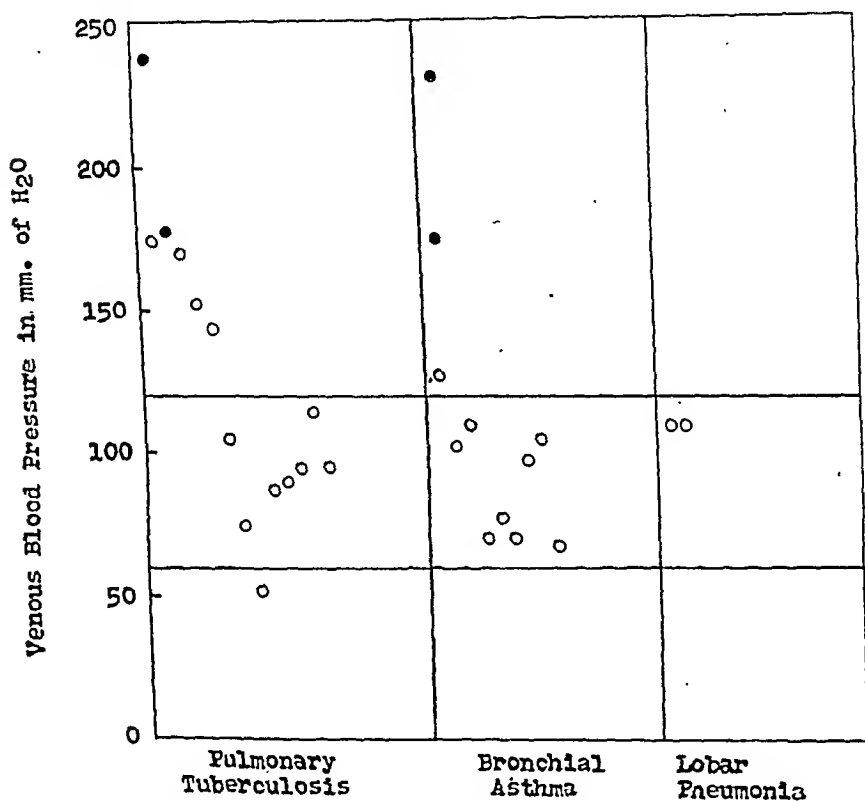


CHART 6.—Behavior of the venous blood pressure in diseases of the respiratory system. The symbols are the same as in Chart 2.

Discussion. The records of a large number of patients have been presented in order to illustrate the value of routine determinations of the venous blood pressure in certain cases. The outstanding finding has been the increase in venous pressure in congestive failure of the heart and in some cases with an aortic aneurysm or other mass within the mediastinum. The venous pressure in these conditions has been sufficiently high to stand in marked contrast to the normal pressure in diseases in which circulatory failure did not occur. This relation held in disorders of the respiratory system as well as for cases with hypertension. Whenever a high venous

pressure was discovered, unless due to a mediastinal mass, it indicated a failing heart and constituted one of the early signs of congestion.

There are always on hospital wards cases which present exceptional problems of diagnosis. In these patients a venous pressure determination may be of much help. It will be recalled that an increased venous pressure in 3 of the cases with aortic aneurysm

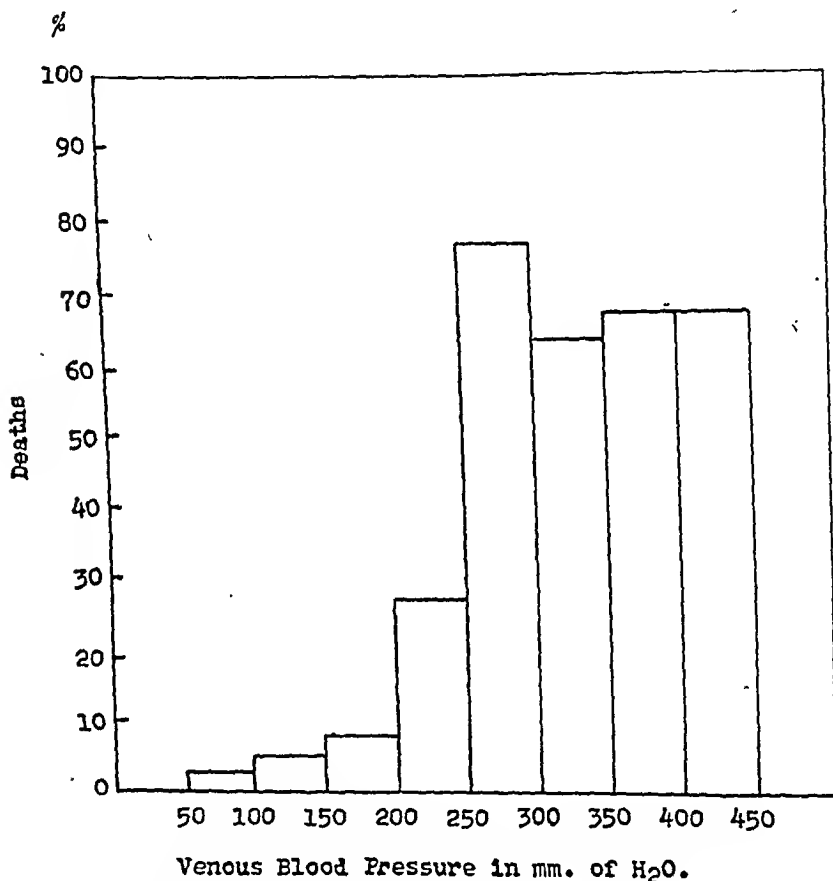


CHART 8.—Distribution curve for the deaths from all causes. Note the marked increase in mortality when the venous pressure was above 250 mm. of H₂O.

was the first indication of a lesion of the circulatory system. The importance of knowing the venous blood pressure was further emphasized by the chance admission on the same day of 3 patients in coma and with signs of a cerebral lesion on the right side. In the first 2 patients the venous pressure was normal and a diagnosis of brain tumor was made. At necropsy, 1 case was found to have a glioma in the right frontal lobe and the other an abscess in the same region. When the third patient was admitted with similar findings, the same diagnosis was made. However, in this case the

venous pressure was elevated on 2 occasions (183 mm. and 210 mm. H₂O) and it was suggested that the patient was suffering from circulatory collapse. The patient died shortly, and at the autopsy the coronary arteries were seen to be completely occluded, the right side of the heart was greatly dilated, the lungs were edematous, and the liver the seat of chronic passive congestion. The brain was normal in appearance.

The value of serial determinations of the venous blood pressure in estimating the efficiency of therapeutic measures has been stressed by many writers.¹¹⁻¹⁶ The results of this study have amply justified this attitude. There is no other procedure which so easily and accurately affords an estimate of the cardiac reserve in disease.

The prognostic significance of venous pressure measurements has been unfortunately neglected. In Chart 8 the death rate from all causes has been plotted, the highest venous pressure reading for each case having been used in the calculations. The striking feature of the results is the great increase in mortality when the venous pressure rose above 250 mm. H₂O. Among the patients with a venous pressure of 250 mm. H₂O or higher the mortality was 69%, whereas it was only 8% among those whose pressure remained below the critical level of 250 mm. H₂O.

In conclusion a few personal remarks may be permitted. The recent journals contain many excellent papers which indicate the value of measuring the venous blood pressure in patients with cardiocirculatory disease; but in spite of the unanimity of opinion, full advantage has not been taken of this valuable test. The technique is easy; the normal range and behavior of venous pressure in disease are well known. Perhaps the inertia is to be explained by a natural hesitancy to accept procedures which are not customary. However, a cure for the disease is easily effected by learning the technique of the test and applying it in suitable cases. The results of "taking the cure" have been once more described. We have been so impressed with the value of the test that venous pressure determinations are now made on all cardiac cases admitted to the medical service.

Summary. 1. The results of 366 determinations of the venous blood pressure in 215 patients suffering from various diseases have been presented.

2. In a control series of 31 patients who showed no evidences of circulatory disease, the average venous pressure was 83 mm. H₂O and the difference of the two readings with the standard deviation of the difference was 16 mm. H₂O \pm 11 mm. H₂O.

3. An increase in venous pressure was observed only in patients suffering from cardiac failure with congestion or mediastinal obstruction.

4. Serial determinations of the venous pressure were of value in following the course of cardiac cases; a shift towards the normal indicated a favorable prognosis, but a progressive increase in pressure was an unfavorable sign.

5. The arterial and venous blood pressures appear to be independent, in the sense that a change in one does not necessarily affect the other.

6. The presence of pulmonary tuberculosis, bronchial asthma or lobar pneumonia did not influence the venous pressure of the cases studied.

7. When an increase in venous pressure occurred in any disease, it usually indicated beginning circulatory failure.

8. Of the patients with a venous pressure over 250 mm. H₂O, 69% died within 3 months, whereas only 8% of those with a pressure below this critical level succumbed.

In the preparation of this paper I have profited greatly from the kind criticism of Dr. Edward L. Bortz, Chief of Medical Service "B," the Lankenau Hospital. On his service this work was initiated and largely carried to completion. Dr. Fred L. Hartmann, Chief of Medical Service "A," has placed the records of several of his patients at my disposal.

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THE DEMONSTRATION OF COLLATERAL VENOUS CIRCULATION IN THE ABDOMINAL WALL BY MEANS OF INFRA-RED PHOTOGRAPHY.

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INFRA-RED photography has been used experimentally, mostly in astronomy, for many years. Only recently the production of plates that are sufficiently sensitive to the infra-red rays to permit short exposures has made possible the use of this method on a wider scale. Clark¹ says that this method of photography has been found of value in certain European hospitals as a diagnostic aid in certain types of skin diseases. He also records that European workers have found that varicose veins which were not visible to the eye have been demonstrated by this method. Recently Barker and Julin² and Payne³ have shown the value of this technique in demonstrating the superficial venous system of man. Payne concludes that veins can be made visible by this means when they cannot be seen nor recorded upon the ordinary photographic plate. On the other hand Barker and Julin believe that it is doubtful if veins can be shown by infra-red plates which cannot be seen by the naked eye. These authors credit Rawling with the suggestion that infra-red photography might find some application in medicine. To him is also attributed the finding that the skin has its maximum transmission in the part of the spectrum wherein are found the infra-red rays. This fact together with the fact that the blue color of the veins is absorbed by the filter used in the infra-red technique and thus made to appear dark on the infra-red (positive) plate, explains why the veins can be so graphically demonstrated by this method of photography.

In view of the excellent portrayal of superficial veins by this method it seemed to us to be worthwhile to attempt some use of this procedure in the hope that it would aid in the early recognition of the collateral circulation in cases suspected of early portal obstruction. As this is a frequently debated question, we have photographed the abdominal wall in a number of cases in which this question arose.

Case Reports. I. CASES WITH PROVED CIRRHOSIS.

CASE 1.—M. B., a white woman, aged 47, entered Strong Memorial Hospital with the complaint of enlargement of the abdomen and loss of weight. The history records two attacks of painless jaundice during the preceding year and the loss of about 20 pounds in weight during this time.

There were definite signs of fluid in the abdomen. After paracentesis the liver edge was felt slightly below the costal margin. The spleen was not palpable. One observer noted enlarged superficial veins in the abdominal wall. A diagnosis of cirrhosis of the liver was considered most likely, although the attacks of painless jaundice which had cleared up suggested the possibility of obstruction of the common bile duct by a stone. The venous network could not be seen in an ordinary photograph of her abdomen; an infra-red photograph (Fig. 1) revealed evidence of venous distention out of proportion to that seen by the naked eye. The patient became comatose and died 17 days after admission. An autopsy revealed extensive cirrhosis of the liver. There is no statement about the state of the veins in the autopsy record.



FIG. 1.—Infra-red photograph of abdomen of patient with proved cirrhosis of the liver.

II. CASES WITH PROBABLE CIRRHOSIS.

CASE 2.—A. M., a white woman, aged 50, entered Rochester Municipal Hospital with the complaint of weakness and loss of weight for about 1½ years. Because of language difficulties no adequate history was obtained. The significant findings were: evidence of recent weight loss, deep jaundice, a greatly enlarged liver, a barely palpable spleen and ascites. The liver edge was palpable slightly below the level of the umbilicus; it was firm, questionably finely nodular and not tender. Moderate distention of the superficial veins of the abdominal wall was noted by several observers. A diagnosis of cirrhosis of the liver seemed most likely although metastatic infiltration of the liver from some intraabdominal neoplasm was recognized as a possibility. Roentgenologic studies of the gastro-intestinal tract revealed no evidence of neoplasm. An ordinary photograph (Fig. 2) of this patient's abdomen revealed nothing at all in the way of veins; an infra-

red photograph (Fig. 3) revealed strikingly the pattern of the superficial veins, the largest and most numerous of which were in the flanks. The patient gradually became comatose and died. Permission for autopsy was not obtained.

CASE 3.—G. H., a 62-year-old white man, who had been a heavy drinker for many years, was admitted to the Rochester Municipal Hospital with the complaint of enlargement of the abdomen for a period of a month. After paracentesis a hard liver edge could be felt about 5 cm. below the costal margin. The spleen was not felt. One observer made the note that there was no evidence of collateral circulation in the abdominal wall, while a second observer on the same day made the note that there were definitely visible veins forming a caput Medusæ about the umbilicus. An infra-red



FIG. 2.—Ordinary photograph of abdomen of patient suspected of having cirrhosis of the liver.

photograph (Fig. 4) showed the veins to be definitely more visible than those seen in any normal abdomen. The diagnosis of cirrhosis of the liver seemed highly probable. The patient was discharged from the hospital with instructions to return at intervals for abdominal paracentesis.

CASE 4.—M. F., a white woman, aged 52, was admitted to the Rochester Municipal Hospital with the complaint of a sensation of epigastric fullness for a period of about 13 weeks. The history was quite inconclusive. The only physical finding of apparent value was a considerably enlarged liver which felt firm and smooth. There was no visible evidence of enlarged collateral veins in the abdominal wall. An infra-red photograph, however, showed them to be considerably more extensive than in our controls. She was discharged in the same condition as on admission.

CASE 5.—C. P., a 46-year-old white man, entered Strong Memorial Hospital with the complaint of pain across the upper abdomen for 3½ years. Associated with this he had had varied complaints of indigestion. There



FIG. 3.—Infra-red photograph of abdomen of same patient as in Fig. 2.



FIG. 4.—Infra-red photograph showing an increase in number and size of veins in a patient suspected of having hepatic cirrhosis.

was a history of tarry stools at onset of his illness. Physical findings were essentially negative. However, a Roentgen ray of his abdomen revealed that the spleen was enlarged and that the liver appeared to be smaller than normal. The patient then recalled that at one time his family physician had told him that there was a mass lying to the left of his stomach. The spleen was not felt by us, however. There was no visible evidence of increased collateral venous circulation noted, but an infra-red photograph showed venous channels more extensive than those of our controls. The patient was discharged from the hospital unimproved.

CASE 6.—J. S., a 55-year-old Italian man, was admitted to the Strong Memorial Hospital with the complaint of stomach trouble. This began 3 months before admission and consisted of soreness in the right upper part of his abdomen and frequent vomiting, the vomitus at times containing small amounts of bright blood. There was the history of wine taken with his meals for many years; no other alcohol. The essential physical findings consisted of a firm, smooth liver edge felt about 7 cm. below the right costal margin and a spleen which was barely palpable. There was no icterus. There was no evidence of abnormal venous distention of his abdominal wall. A diagnosis of cirrhosis of the liver was made. An infra-red photograph of his abdomen showed more venous channels than would be expected in a normal individual. However, these were not as marked as those seen in other cases.

III. CASES WITH ENLARGED LIVERS FROM OTHER CAUSES.

CASE 7.—H. B., white male, aged 60, entered Rochester Municipal Hospital with the chief complaint of swelling of the legs of 3 weeks' duration. He had been dyspneic for several years. History of an attack of painless jaundice lasting about 2 weeks, $2\frac{1}{2}$ years before admission. The stools had been tarry for several days. Physical examination revealed considerable edema of both ankles, a few coarse râles at the right lung base, slight enlargement of the heart to the left, a blood pressure of 170/80 and an enlargement of the liver, which at the time of admission extended about 5 cm. below the costal margin. The edge was firm and not tender. There was questionable evidence of ascites. No evidence of collateral venous circulation was seen. A diagnosis of cirrhosis of the liver and of hypertensive and arteriosclerotic heart disease was made. An infra-red photograph of the abdomen revealed no evidence of any increase in the collateral venous circulation. Routine treatment of congestive heart failure resulted in a definite diuresis with decrease in the size of the liver until the edge was no longer palpable. The patient's condition improved and he was discharged to go home with but slight evidence of congestive heart failure. No cause for the tarry stools was found.

CASE 8.—M. M., a single white woman, aged 56, was admitted to the Rochester Municipal Hospital because of weakness and loss of weight over a period of about 8 weeks. Very little else pertaining to her history could be obtained. On physical examination the abdomen was found to be greatly distended and there was a large, irregular, hard mass filling the epigastrium. The liver edge was easily felt just below the umbilicus. It was rough, moderately firm and slightly tender. Carcinoma of the stomach with metastases to the liver was the diagnosis made. No evidence of collateral circulation was apparent clinically. An infra-red photograph likewise showed nothing of this nature. She failed progressively and died. Autopsy examination showed a carcinoma of the ascending colon with metastases to the liver.

CASE 9.—G. E., a 65-year-old white man, had been admitted to the Strong Memorial Hospital 17 times over a period of 19 months for treatment of congestive heart failure. His liver had been enlarged throughout practically this entire period. No evidence of collateral circulation had

been apparent on his abdominal wall at any time. An infra-red photograph taken at a time when his liver reached almost to the level of the umbilicus showed no dilated veins. He is still returning at intervals for treatment.

Another case is reported to emphasize further the possible diagnostic value of this method.

CASE 10.—F. M., a white married woman, aged 34, entered the Rochester Municipal Hospital with the complaint of recurring attacks of right upper quadrant pain associated with jaundice over a period of 8 years! During this time she had passed tarry stools at times and gave the history of recent vomiting of bright blood. Eight years before this admission while convalescing in this hospital from scarlet fever, she developed upper abdominal pain and jaundice. Cholecystectomy was performed at this time. No stones were found in the gall bladder; the common duct was not explored because of operative difficulties. At the time of her last admission there was nothing found of any apparent significance on physical examination. No icterus was apparent, but a report of her icterus index from the laboratory was 20. The question arose as to whether she had cirrhosis of the liver or common-duct obstruction, possibly from a stone, as the cause of her complaints. No evidence of collateral circulation on her abdominal wall was apparent. An infra-red photograph also failed to show any such evidence. Because of the possibility that she had an obstruction of the common bile duct, an exploratory operation was performed which revealed absolutely nothing abnormal. The common duct was opened and probed. The liver appeared to be entirely normal in size and consistency. During her postoperative convalescence, the patient finally confessed that at least the majority of her complaints were feigned because of unpleasant home conditions.

Comment. From our small series of cases it would appear that infra-red photography offers a better means of demonstrating the collateral venous circulation in the abdominal wall than is afforded by any usual clinical method. In 4 cases in which a diagnosis of cirrhosis of the liver was made, photographic evidence of an increased venous pattern was found, though the diagnosis was confirmed at autopsy in only 1 case. Clinical evidence of collateral circulation was apparent in 2 of these cases, was questionable in another and was absent in the fourth. From this we are inclined to agree with Payne that the infra-red technique will demonstrate, in some cases, veins that are not visible to the naked eye. In every case in which an increased degree of venous distention was apparent both on the photograph and by direct inspection, it was by the former that the abnormality was better shown. In Case 2, this disparity was most marked; only moderate venous enlargement was apparent to the eye while the infra-red photograph showed this in striking degree. Case 5 is of interest in that cirrhosis of the liver was suggested by the history while there were no physical signs elicited to substantiate this diagnosis. However, an abdominal Roentgen ray suggested an enlarged spleen and a small liver and there was reason to believe that the spleen had been felt on one occasion. Interestingly enough in this case an infra-red photograph showed what was taken to be an abnormal degree of venous distention. In this type of case, if such a diagnosis is later established, it would

appear that infra-red photography, by demonstrating collateral circulation which was clinically not apparent, is of definite value.

Of a somewhat similar nature is Case 4. Here there was an indefinite history of abdominal discomfort and the only definite physical finding of a positive nature was an enlarged liver. The infra-red photograph showing an increased venous pattern suggests that this patient had some degree of portal obstruction. It is only by continued study of such cases as these last two that conclusions as to the significance of these findings will become apparent. This we intend to do.

In Case 10, negative findings with regard to evidence of collateral circulation both clinically and from an infra-red photograph may be of equal value with positive findings in other cases. Here, where there was the question of cirrhosis of the liver or common bile-duct obstruction, if the former could be excluded an exploratory operation would appear indicated, while if evidence pointing to cirrhosis were obtained the patient should be spared useless surgery. Such evidence we believe may be afforded by an infra-red photograph. In this particular case there was no evidence of portal obstruction at operation.

That liver enlargement *per se* does not produce signs of collateral circulation as judged by our standards, is clearly shown by the photographs of the abdomens of 2 patients with congestive heart failure and large livers, and another patient with a large liver resulting from carcinoma infiltration. No evidence of collateral circulation was apparent to the eye in any of these.

Occasionally, as in Case 7, it is necessary to attempt to decide whether an enlarged liver is due to congestive heart failure or to cirrhosis of the liver. In this case negative evidence from an infra-red photograph of the abdomen as well as from inspection, tended to rule out cirrhosis. The subsequent shrinkage of the liver coincident with a moderate diuresis during routine treatment for congestive heart failure seemed to exclude cirrhosis.

It is further conceivable that in cases of Banti's syndrome and other similar conditions where splenectomy is contemplated, information relative to the possibility of associated hepatic lesions, so frequently found, may be afforded by infra-red photography. If collateral circulation can be demonstrated on the abdominal wall damage of the liver sufficient to cause some degree of portal obstruction is probably indicated. Of course portal obstruction outside of the liver might well be expected to give the same findings with regard to venous distention. Obviously this knowledge would be of value in deciding on the probabilities of success from splenectomy.

Summary. Ten cases are presented in which there was evidence or suspicion of hepatic disorders. Clinical findings with regard to evidences for or against associated portal obstruction, as shown by the demonstration of collateral circulation on the abdominal wall.

are given. Comparison is made between the clinical findings and those obtained from ordinary and infra-red photographs of the abdomens of the patients presented. These data seem to indicate that infra-red photography may be of value in demonstrating degrees of collateral circulation which are not detected by usual clinical methods. At least it is an excellent means of recording abnormal degrees of superficial venous distention. Suggestions as to further application are made.

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STUDIES OF PERIPHERAL VASCULAR PHENOMENA.

IV. THE EFFECT OF ARTIFICIAL FEVER ON THE PULSE VOLUME CHANGES OF THE FINGER.

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SINCE the introduction of fever therapy in the treatment of disease there has been a renewed interest in the physiologic changes which occur during artificial fever. It is well known that in the fever of disease and in experimental and therapeutic fever, marked changes in the normal physiologic mechanisms occur, such as changes in the composition and volume of the blood, the cardiovascular system, and the irritability of the central nervous system. It is not within the scope of this paper to discuss these changes except as they are related to the problem at hand, namely, the study of peripheral vascular changes during artificial fever, and its effect upon the body in general.

Furthermore, we are aware of the fact that there are controversial points with regard to fever therapy such as: (1) The best methods of inducing artificial fever; (2) the degree of fever to be used; (3) the length of time the fever should be given.

This work has brought out many points of interest bearing upon these controversial points and we shall comment upon them briefly in the discussion.

Method. This study was made upon 2 individuals: (1) a normal control and, (2) a patient with rheumatoid arthritis. In addition clinical observations were made on a number of other patients during fever treatments.

In each experiment upon these individuals the blood pressure, respiration, heart rate and circulatory changes were measured at frequent intervals; *i. e.*, every 15 minutes to $\frac{1}{2}$ hour. In addition, the rectal temperatures were recorded by a Brown Recording Resistance Thermometer. The circulatory changes were measured in one finger by a device previously described by Johnson¹—an air conduction plethysmograph using colored alcohol for recording. Permanent calibrated records are made photographically on electrocardiograph paper, and estimation of finger volume change can accurately be measured to 0.002 cc. change. We interpret these changes as giving an index of the peripheral circulation (see Johnson,¹ Johnson, Scupham and Gilbert,² and Scupham and Johnson.³)

In each experiment artificial fever to approximately 104.5° F. was induced and maintained for about 8 hours. The interval between each fever treatment depended upon the patient's clinical condition, but in most instances was about 1 week. One 8-hour control period was run during which no treatment was given.

Artificial fever was induced by the following methods: (1) Radiant heat—electric light cabinet; (2) radiant heat—infra-red; (3) hot water bath; (4) diathermy; (5) very high frequency oscillator; (6) foreign protein.

The fever was maintained during the course of the experiment by means of a zipper bag which prevents heat loss and can be removed rapidly in case of emergency, *i. e.*, if heat exhaustion or heat stroke occur. Means for giving emergency treatments were available at all times.

LEGENDS FOR FIGS. 1, 2, 3 AND 4.

FIG. 1.—Finger-volume changes during artificial fever periods. The record on the left is the control and the record on the right shows the effects of fever induced with a hot-water bath and maintained by prevention of heat loss. Note the minor variations in the control record as compared with the marked changes occurring during fever. Also note that the maximum excursions occurred at 103.8° F. while the maximum temperature used was 104.6° F. We interpret the increased volume changes of the finger as increased circulation.

FIG. 2.—The effects of artificial fever induced with external heat and maintained by the prevention of heat loss on the pulse, respiration, blood pressure and circulation. In the 1 case the radiant heat from the ordinary electric-light cabinet was used and in the other from the infra-red. Aside from minor variations the two records are not significantly different. In the experiment as shown by the record on the right the patient did not feel well, and we did not run the fever as high as in most experiments.

FIG. 3.—The results of artificial fever induced with foreign protein on the pulse, respiration, blood pressure and circulation. Note the primary vasoconstriction associated with the chill followed by a vasodilatation. The results of artificial fever on the peripheral circulation differ in this respect from those obtained with artificial fever induced with the application of external heat.

FIG. 4.—The effect of fever as induced by foreign protein upon the volume changes of the third finger of both hands 1 month after sympathectomy. It is noted that a striking change is obtained in the third finger of the control hand but virtually no change in the volume changes of the third finger of the sympathectomized hand. It is also to be noted that in the control hand, skin temperature and heart rate roughly parallel the volume changes of the finger. Very little change was observed in the sympathectomized hand. This indicates that vasodilatation of foreign-protein fever is chiefly of central origin.

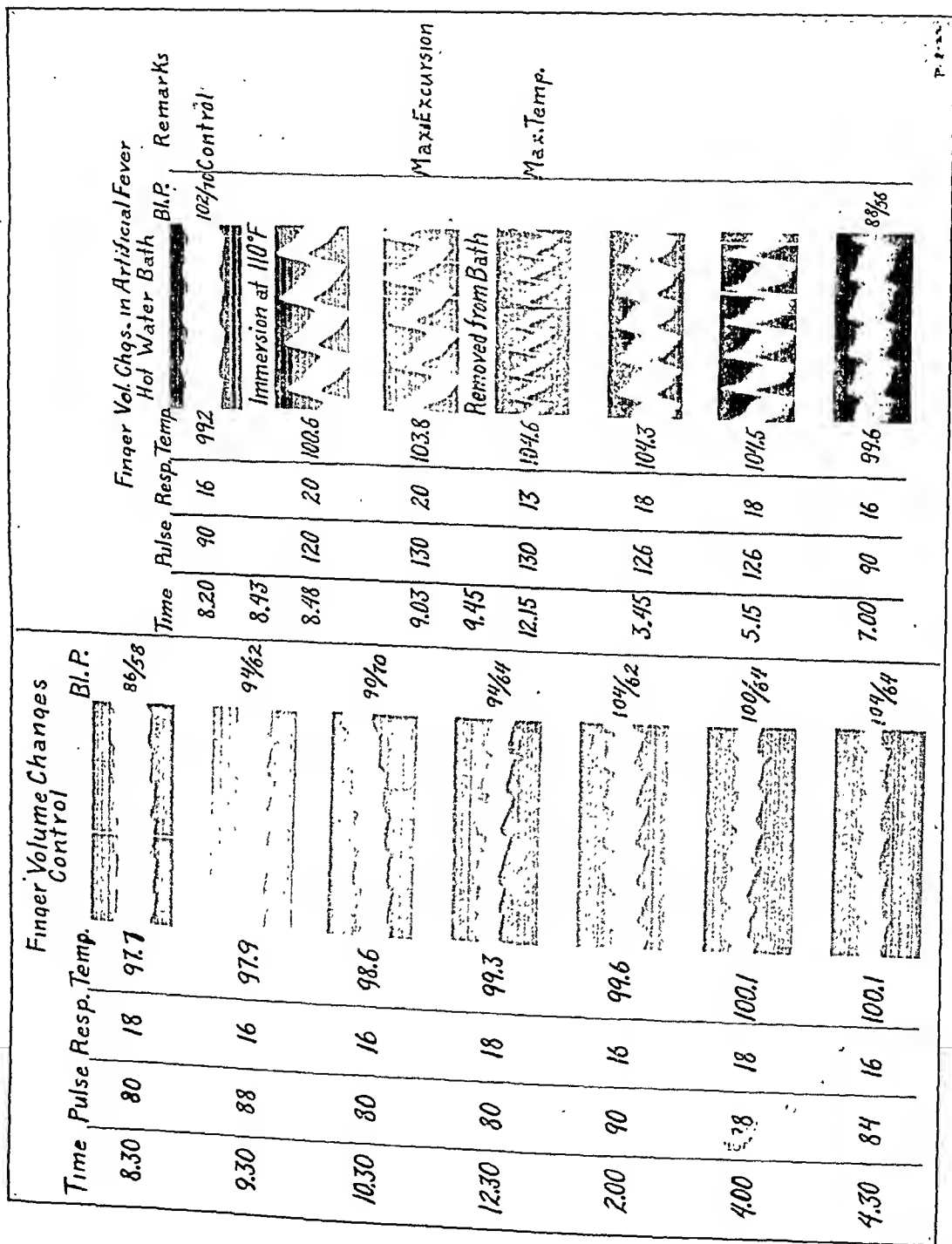


Fig. 1

Finger Vol. Chqs. in Artificial Fever Light Cabinet				Finger Vol. Chqs. in Artificial Fever Radiant Heat - Infra Red			
Time	Pulse	Resp. Temp.	Remarks	Time	Pulse	Resp. Temp.	Remarks
8.20	70	16	98.6	8.30	78	16	99.4
8.25				9.10			99.4
9.15	120	14	101.6	9.45			99.4
9.45	124	14	104.4	10.00	108	20	101.5
9.45				10.30	110	20	102.4
12.00	140	14	104.3	12.15	100	18	101.6
6.00	122	16	102.7	2.15	100	16	102.1
7.45	82	16	99.1	7.15	94	16	99.2

FIG. 2

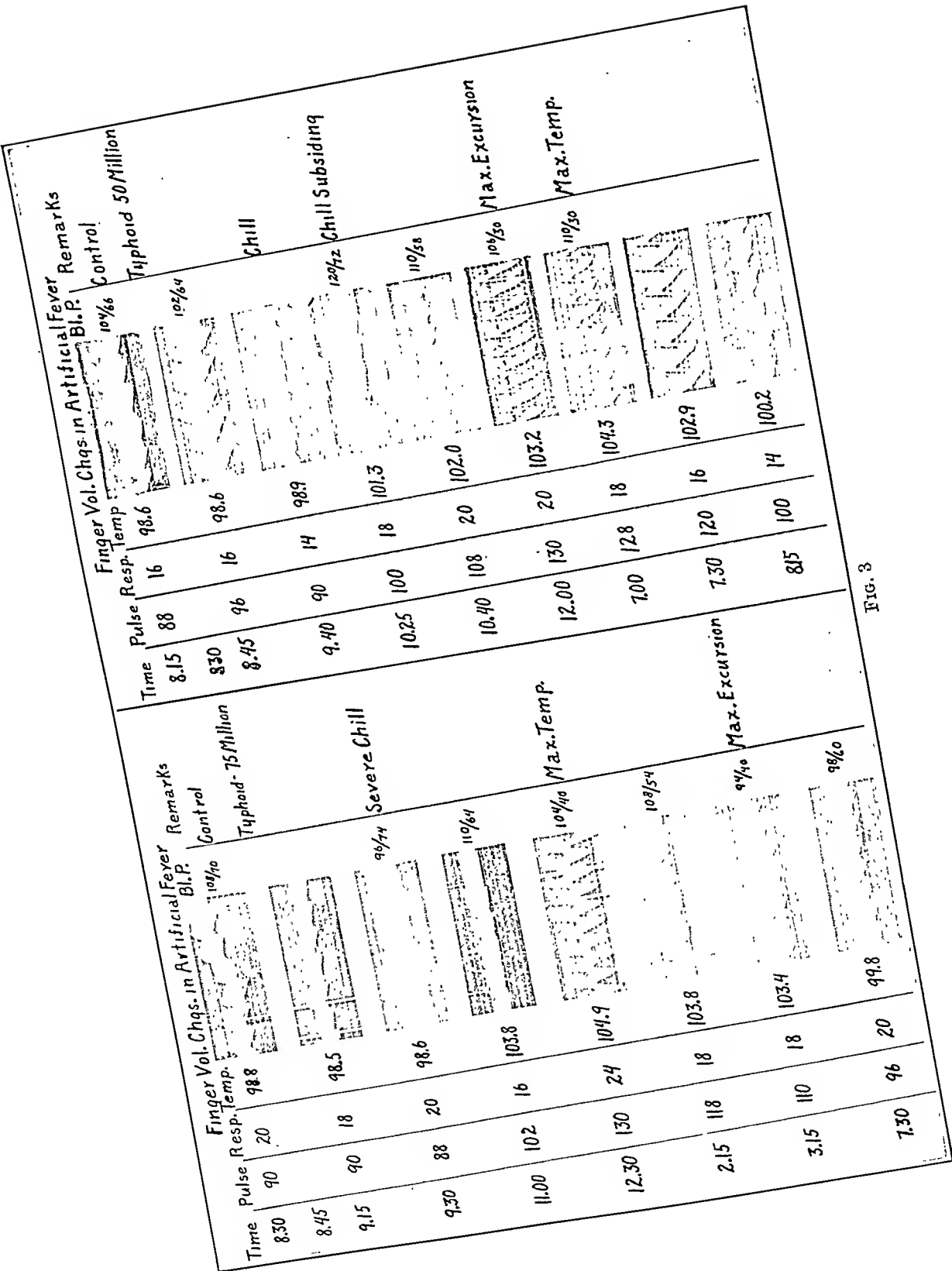


FIG. 3

TIME	VOL. CHGS. 3RD FINGER LEFT HAND-CONTROL	TEMP.		HT.	VOL. CHGS. 3RD FINGER RT. HAND-SYMPATHECT.
		SKIN C	MOUTH F		TH. BL. P T _o
18-32 945A		28.4	98.6	90	35
10	TYPHOID 20 MILLION				
12M		29	100	123	35
1		36.3	101.4	129	35
2		34.7	100.4	120	35
3		35	100	117	35
4		35	99.6	120	35
5		35	99	117	35
7		34.7	98.4	96	34.7
18-32 9A		34.7	98	90	34.4

Results. The results may be tabulated as follows:

1. *Pulse-Volume Changes in the Finger.* A. There was a marked increase in the pulse-volume change in the finger with all types of artificial fever used except foreign protein in which a primary decrease occurred followed by an increase.

B. The maximum increase in pulse-volume change occurred at a temperature lower than the maximum used; i. e., between 103 to 104° F.

C. The pulse-volume change fluctuated in amplitude after the maximum was reached.

D. The pulse-volume change remained above the control level throughout the experiment except with foreign protein as indicated above.

2. *Blood Pressure Changes.* As a rule, in normal individuals, there is a rise in the systolic pressure and a fall in the diastolic pressure during artificial fever, but in this patient there was not much change in the systolic pressure, but a rather marked fall in the diastolic pressure.

3. *Pulse Rate.* As a general rule this is increased during artificial fever.

4. *Respiration is also increased during fever.* As mentioned above the changes observed during the various types of artificial fever used, were essentially the same except with foreign protein and to save added illustrations we are only including typical records showing the phenomena indicated.

Figure 1A shows a control record taken for 8 hours. This has only minor fluctuations in the pulse-volume changes during the course of this period. In marked contrast to this, Figure 1B shows the tremendous increase in the pulse-volume changes when the body temperature is increased by immersion in hot water. These results of increased circulation from this procedure compares favorably with the results obtained in the arm by Hewlett, Van Zwaluwenburg and Marshall⁴ with a different method. It will be seen that the maximum excursion occurred at 103.8° F. while the maximum temperature used was 104.6° F.

Figures 2A and 2B show two similar experiments except that the body was placed in a light cabinet. In the one experiment Figure 2A the ordinary radiant heat was used while in the other infra-red radiant heat was used. Both experiments showed marked increase in circulation.

Figure 3A shows the effect of artificial fever induced with foreign protein (typhoid injections) on the peripheral circulation. Both experiments show a primary vasoconstriction and in this way differs from the fever induced by other methods.

Figure 4 shows a similar experiment upon a patient with a unilateral cervical and upper dorsal ganglionectomy and ramisectomy. The control⁴ side showed results similar to Figures 3A and 3B while

on the operated side no change was apparent. This patient showed a normal response to local heat on the control and operated side. For further details see Johnson, Scupham and Gilbert.²

Table 1 is a summary of the work showing that in general the maximum excursions occurred at temperature considerably lower than the maximum temperature used. This we interpret to mean that the maximum circulation occurs at a lower temperature than the maximum temperature used.

TABLE 1.—FINGER-VOLUME CHANGES WITH DIFFERENT TYPES OF ARTIFICIAL FEVER.

	Control.		Max. amplit.		Max. temp. used.		Final record.	
	Amplit.	Temp.	Amplit.	Temp.	Amplit.	Temp.	Amplit.	Temp.
Radiant heat, electric light cabinet	0.013	99.5	0.045	103.4	0.030	104.6	0.022	99.4
Radiant heat, electric light cabinet	0.010	98.6	0.052	104.3	0.038	104.4	0.009	99.1
Radiant heat, infra-red	0.027	99.4	0.052	102.1	0.047	102.4	0.010	99.2
Radiant heat, infra-red	0.010	98.2	0.080	103.4	0.071	104.4	0.026	99.0
Hot water bath	0.010	99.2	0.060	103.8	0.048	104.6	0.020	99.6
Diathermy	0.013	98.0	0.054	103.4	0.032	104.7	0.043	102.6
High frequency oscillator	0.013	98.2	0.070	104.2	0.055	104.7	0.029	99.7
Foreign protein	0.013	98.6	0.052	103.7	0.042	104.4	0.015	99.5
Foreign protein	0.012	98.8	0.043	104.9	0.043	104.9	0.018	99.8
Control	0.008	97.7	0.016	99.6	0.010	100.1	0.010	100.1

The amplitude is measured in cubic centimeter volume change of the finger and the temperature is the rectal temperature.

This table illustrates that in the majority of the experiments that the maximum finger-volume changes occurred at a temperature considerably below the maximum temperature used. We interpret this as meaning that the maximum circulatory changes occur at the lower temperatures, and that there is an optimum temperature for the maximum circulatory change.

Discussion. These results show an increased pulse-volume change with all types of the artificial fever used except foreign protein which gave a primary decrease of the pulse-volume change which was associated with the chill.

We interpret the increased pulse-volume change as increased circulation as a result of the vasodilatation and probably increase cardiac output. As mentioned in a previous report we indicated that the interpretation of the pulse-volume change is open to some question and also that the same factors which maintain blood pressure in addition to the resistance of the soft tissues in question as the important factors in determining the extent of the excursion. It might be possible to have an increased circulation without increased pulsation but not possible to have an increased pulsation without increased circulation. In these experiments the excursion was markedly increased during the course of the fever except in those experiments where foreign protein was used to promote the fever.

The effect of artificial fever upon the peripheral circulation when induced by general heat with prevention of heat loss was about the same with all of the methods used (Table 1). The finger volume change increased from about 0.01 cc. control to 0.06 to 0.08 cc. The striking feature is that the maximum circulatory response occurred at temperatures considerably lower than the maximum used. Furthermore, the amplitude of the excursions measuring the circulatory response showed marked variations as the temperature was maintained which we interpreted as due to instability of the vasomotor system, and instability of the heat regulating mechanism which is intimately associated with the vasomotor system. These results indicate that there may be an optimum temperature at which a maximum circulatory response occurs. This suggests that high therapeutic fevers up to 106° as often used are too high unless factors other than circulation play a rôle and are only brought out by fevers above the optimum.

That factors other than circulation are important in therapeutic fever are indicated by another very interesting observation in this study:

The circulatory response to artificial fever induced with foreign protein differed from those obtained with artificial fever induced by external heat. Foreign protein uniformly in 5 patients gave a primary vasoconstriction associated with the chill and followed by a vasodilatation. The vasodilatation was never as great as that produced by the other methods unless heat loss was prevented by insulating the body and the fever maintained. Clinically good results are obtained with foreign protein therapy in spite of the fact that the peripheral circulatory response is not as great with fever induced by other methods.

The fundamental difference in the results of the two types of artificial fever, *i. e.*, the foreign protein fever and that produced by external heat, is that the vasoconstriction and vasodilatation of foreign protein fever is probably of central origin, while the vasodilatation with fevers produced by the other means is chiefly of peripheral origin. For further details see the article by Johnson, Scupham and Gilbert.²

In this work a number of clinical observations were made which are worthy of mention:

Artificial fever induced by external heat is dangerous unless proper precautions are taken and even then some patients do not tolerate fever well, particularly those with impairment of the cardiovascular system.

First, one should have proper equipment. A recording thermometer should be used so that an accurate observation of the temperature can be had at all times. A physician should be present at all times and means for emergency treatment of heat exhaustion should be available.

The ability to tolerate this type of artificial fever seems to be related to the cardiovascular reserve. Some patients under mild fever will develop symptoms of cardiac insufficiency such as dyspnea, cyanosis and the respirations will be markedly increased. In 1 case auricular fibrillation started at 102° (rectal temperature). Another patient vomited for a week after fever of 101° for 2 hours while a third patient persistently had convulsions with temperatures around 104°. These illustrations merely show that: (1) arbitrary standards of treatment cannot be fixed for this type of therapy and, (2) the patient requires constant attention from a physician to minimize the danger.

The question of how long the fever should be maintained is debatable. We feel that it should not be run to the point of exhaustion. This will vary from patient to patient and treatment to treatment.

Regarding the best method of inducing artificial fever from external heat we can only say that in view of the danger attended with this type of therapy that the safest method should be used. This is probably the ordinary electric light cabinet. The most dangerous method is probably the hot water bath.

We are in agreement with Simpson⁵ that the possibility of doing harm with unskilled workers or trying to carry out this treatment with inadequate equipment is perhaps greater than the possibility of doing good. We also feel that more fundamental work dealing with physiology of fever is essential before this procedure can be carried intelligently.

Summary and Conclusion. The effects of artificial fever upon the peripheral circulation have been presented and may be briefly summarized as follows:

1. There was a marked increase in the pulse-volume changes of the fingers with all types of artificial fever used, except foreign protein which gave a primary decrease associated with the chill, but followed by an increased circulation.

2. The vasodilatation of foreign protein fever is probably of central origin while the vasodilatation with artificial fever induced by external heat and preventing heat loss is chiefly of peripheral origin.

3. The maximum increased circulation from artificial fever occurred in general at temperatures between 103 and 104° F. while the maximum temperature used was 104.5°. This suggests that there is an optimum temperature at which peripheral circulation reaches a maximum.

4. Artificial fever from external heat and prevention of heat loss is dangerous and should not be used unless adequate facilities are available and should not be left in the hands of a technician.

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METABOLIC RATES IN THERAPEUTIC FEVER.

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THE parallelism between fever and variations in the metabolic rate is well known. The major part of the work in this field has been done upon patients with febrile diseases such as typhoid, malaria, tuberculosis, erysipelas, etc., and upon patients in whom temperature rise has been produced by means of intravenous proteose and typhoid vaccine.¹⁻⁵ But little work has been done on fever produced by the more recent physical methods. Neymann and Osborne⁶ found an average rise of 7% in the metabolic rate for each degree fever (F) in patients in whom body temperature was raised by means of diathermy current. Nasset and coworkers^{7,8} induced fever in anesthetized dogs by means of diathermy and found an average increase of about 12.5% in the metabolic rate for each degree of temperature (C) rise. In one dog an increase of 313% above basal conditions occurred. No quantitative relationship was found between rise in body temperature and increase in the metabolic rate. The use in this clinic of several methods for the induction of fever in the treatment of central nervous system syphilis permitted a study and comparison of the increases in the metabolic rate obtained by these different methods.

Subjects. Seven male patients were selected from a large group who were given fever therapy. These patients varied from 32 to 46 years; 5 (F. K., A. J., S. M., J. W., J. H.) were diagnosed by clinical and laboratory procedures as general paresis; M. J. as tabes dorsalis with gastric crisis; W. S. as meningovascular neurosyphilis; F. K. was found to have a consistently low basal metabolic rate on numerous repeated tests, but myxedema was not present. All patients were hospitalized during fever therapy, and were given the customary mixed hospital diet.

Methods. Fever was induced by 5 different methods: 1, Diathermy current; 2, electric light cabinet and hot moist air; 3, a method combining (1) and (2); 4, electric blanket; 5, mixed typhoid vaccine intravenously.

In 6 patients fever was induced only by means of the combined method of diathermy current, electric cabinet and hot moist air. Body temperature was raised to 104° to 105° F. in from 60 to 90 minutes and then allowed to fall. In 1 patient, F. K., body temperature was prolonged by this method at arbitrary levels from 1 to 3 hours during which a series of metabolism determinations were obtained. In addition, fever was induced in patient, F. K., by all 5 methods allowing for a comparison of the metabolic rates in fever induced by the different methods in the same individual.

The diathermy machine used is that of the General Electric, Victor type. Insulation was obtained by means of a celotex cabinet, containing eight 60 Watt electric lamps, and by means of rubber and woolen blankets. The latter type of insulation is more uncomfortable than the former. With the electric cabinet insulation the heat given off by the lights is considerable and both dry and wet bulb temperatures rise rapidly, reaching a level of about 115° F. and 100° F., respectively, in an hour. In addition air blankets of different dry and wet bulb temperatures are present as one proceeds from body level to the top (19 inches above) of the insulating cabinet.

Two different sets of electrodes were used for diathermy treatment: 1, fenestrated electrodes applied to chest, abdomen and back and kept in place by means of a canvas jacket and 2, segmented bracelet electrodes encircling both thighs, arms and waist.

The electric blanket is merely an enlarged electric heating pad. The patient, except for the head, is covered with rubber and insulating blankets, and then enveloped in a large electric mesh blanket. The blanket temperature fluctuates from about 115° to 130° F.

Typhoid vaccine fever was induced in patient, F. K., by the intravenous injection of 150 million mixed organisms.

Rectal temperatures were used and were obtained by means of a self-recording motor-driven temperature unit. Where temperature changes occurred during the metabolism test an average reading was taken.

A portable Benedict-Roth metabolism machine was used to determine the metabolic rate over 6- or 7-minute intervals. The DuBois standards as modified by Boothby and Sandiford were followed in the calculation of the results. The initial weight of the patient was taken even though there occurred, as a rule, a loss of from 1 to 5 pounds in weight during treatment, the loss in weight depending upon the duration of treatment and the fluid intake. The changes in weight involved a maximum variation of $\pm 2.5\%$ in the results obtained.

Treatment was usually given every second or third day. On the morning of treatment, a light breakfast was allowed at 6.30 A.M. to 6 patients. This light breakfast consisted largely of carbohydrates, some protein, and very little fat. The seventh patient, F. K., was able to undergo all fever treatment under basal conditions. At 8.00 A. M. the patient was weighed and then allowed a rest period in bed of from 45 to 75 minutes. An initial metabolic rate was then determined and in the case of patient F. K., repeated. Fever treatment was then started.

Results and Discussion. The initial metabolic rates obtained on each patient before the start of fever therapy on each treatment day revealed fluctuations of from 15% to 35% (Chart I). In 4 of the 7 patients greater variations than the usually accepted $\pm 10\%$ for one's basal metabolism were present and may well be due to the effect of the early morning meal which though restricted was not

uniform. No attempt was made to estimate quantitatively the intake of food, but since metabolic determinations were not made for from 2 to 2½ hours after the light breakfast allowed, the effect of food was probably slight and became less so as body temperature was rising. Soderström and coworkers⁹ have shown that a light breakfast of 222 calories consisting of one slice of bread (30 gm.), 60 cc. milk, and 8 gm. of butter (a breakfast consisting of 4.7 gm. protein, 9 of fat, and 28.9 of carbohydrate) increased heat production only 7%, 2%, and 2%, the first, second and third hour respectively after ingestion. The initial metabolic rates of patient, A. J., who was allowed an early breakfast, and who could best tolerate fever therapy showed the least variation (15%). The greatest fluctuation in the initial metabolic rates occurred in patients, S. M., and M. J., who were the most uncomfortable and restless during fever therapy. Patient F. K., under basal conditions, showed variations of 20% in the basal metabolic rate on 47 determinations. When the rates of this patient were taken chronologically, it was seen that repeated fever therapy over a period of 7 months had no residual effect on the basal metabolic rate.

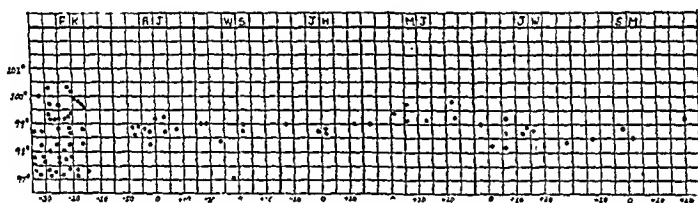


CHART I.—Initial metabolic rates.

The metabolic rates of the 7 patients during fever induced by diathermy current combined with the electric cabinet and hot moist air are seen in Chart II. As the body temperature was rising rapidly 140 determinations were made and 180 as the body temperature fell after the insulating electric cabinet had been removed. The metabolic rates tended to increase as the body temperature was raised but variations of a marked degree occurred at different temperature levels, whether the body temperature was rising or falling. These variations, as much as 70%, are much more marked when the results of all the experiments are grouped together than when the results of each patient are considered separately. The metabolic rates of the 7 patients during this type of induced fever revealed an average increase of from 5 to 14% for each degree rise of body temperature. Repeated experiments revealed also fluctuations for each patient for similar temperature levels so that the rise in metabolic rate was not absolutely uniform as body temperature increased. The degree of fluctuation appeared to depend to a large extent upon the amount of discomfort present during fever treatment as revealed

especially by hyperpnea and restlessness. Patients, S. M., and M. J., in whom restlessness and hyperpnea were most marked, showed the greatest average increase in metabolic rate, 10% and 14% respectively, for each degree of temperature rise. Patient, A. J., who experienced very little discomfort during fever therapy showed an average increase of only 5% for each degree temperature rise. The effect of hyperpnea and discomfort during fever upon the metabolic rate has already been pointed out by various observers.^{10,11} The removal of the insulating cabinet when body temperature had reached its desired height and the exposure of the patient to room

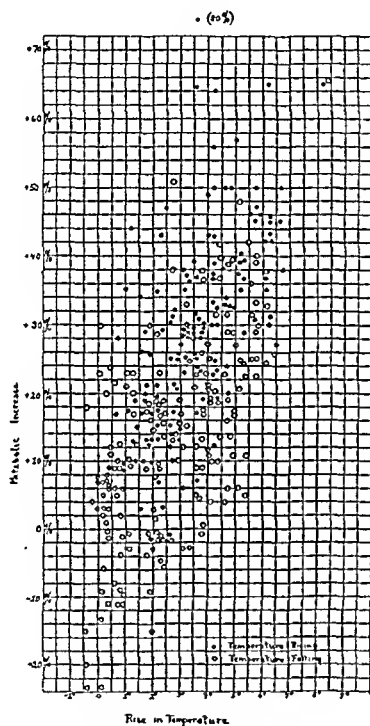


CHART II.—Increase in metabolic rate in diathermy fever.

temperature and humidity was accompanied in most cases by a rather rapid and steep fall in metabolic rate. This occurred whether body temperature remained at the same level, fell, or even continued to rise. Following this preliminary drop, the metabolism tended to fall quite slowly. At times the drop following uncovering of the patient would be so steep that the metabolic rates obtained thereafter even though fever was still present, would not vary much from that obtained at the start of the experiment. As a rule, however, with uncovering, the metabolic rate would fall to a level above that obtained before fever was induced and then fluctuate within narrow limits about this level even though the temperature fell as much as

4° to 5° F. The final metabolic rate obtained at the end of each experiment, when body temperature was nearly or the same as at the start of the experiment, also showed variations from the initial metabolic rates even as much as 30% (Chart II).

Barr and DuBois,² following observations on patients with malaria, have stated that with an increased temperature increased heat production occurs, and that the elimination of heat by means of the expired air and evaporation of sweat from the body surface

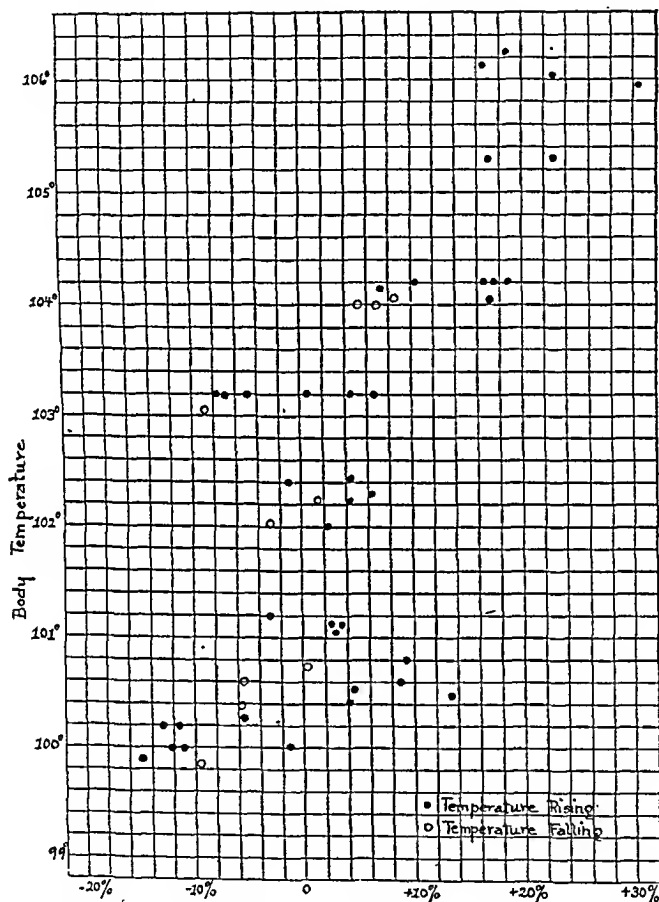


CHART III.—Metabolic rates at sustained temperature levels.

remains fairly constant. With a fall from a higher to a lower body temperature heat elimination through these channels is increased considerably, and heat production tends to fall to a low level slightly above normal. During the fall in body temperature there is no marked decrease in heat production, but a gradual lowering of production to a normal level. According to these observers no mechanism is present by which heat production can be lowered abruptly. The rather rapid and steep drop in metabolic rate occurring after the removal of the insulating box and its hot air blanket

whether body temperature fell, rose, or remained at the same level in the experiments reported above must be attributed not only to the above described mechanism of temperature fall but, also, to the removal of the hot humid air blanket which by itself is capable of producing changes in the metabolic rate whether body temperature is increased or not.^{12,13} The increase in metabolic rate caused by the air blanket is due (a) to the heating of the peripheral body tissues to a temperature above that recorded rectally and (b) to the disturbing effects of a variable degree produced in each individual patient.

When fever was induced in patient F. K. by the combined method of diathermy, cabinet, and moist air, and body temperature prolonged at arbitrary levels, the metabolic rates obtained at these different levels showed a rather suggestive linear relationship to the temperature (Chart III). In these experiments, also, a lower metabolic rate was obtained as a rule when body temperature fell during the determination than when it was rising. The determinations in these experiments were made after the diathermy current had been turned off, contrary to the method used for the determinations shown in Chart II.

It is our experience that metabolic rates obtained as the body temperature rises are usually higher than when obtained at the same or even higher levels after the diathermy current has been turned off. Occasionally the metabolic rate would show a fairly marked drop after body temperature had been maintained at the same level for a few hours. When hyperpnea is present as body temperature is rising rapidly, the turning off of the diathermy current usually results in greater comfort and the disappearance of hyperpnea even though the body temperature remains at the same level or continues to rise.

The question then arises as to whether diathermy current *per se* has any effect upon the basal metabolism and is responsible for some increase in the metabolic rate when this type of fever induction is used. Nasset⁸ altered the kilocycle value of the diathermy current used in dog experiments and concluded that diathermy current *per se* had no specific effect upon the metabolic rate. Repeated metabolism determinations on patient F. K. (Table 1) following short periods of diathermy current, revealed no appreciable effect of diathermy current upon the basal metabolic rate when no change or even very little change in body temperature occurred. Alterations of current frequency at high temperature levels also caused no appreciable changes in the metabolic rate. The differences in the metabolic rate obtained at an increased body temperature before and after the turning off of the diathermy current is due to the disappearance of the hyperpnea and discomfort of the patient and not to any specific effect of diathermy current upon the basal metabolic rate. Similar conclusions were drawn

by Nasset and coworkers.⁷ However, the drop in the metabolic rate in anesthetized dogs at increased temperature levels when the diathermy current was turned off, even though body temperature continued to rise, could not, according to these observers, be accounted for by diminished respiratory activity alone.

TABLE 1.—THE EFFECT OF DIATHERMY CURRENT PER SE ON THE BASAL METABOLIC RATE.

Time.	Pulse.	Body temperature, ° F.	Box temperature, ° F.	Comment.	Metabolic rate.
9:25	74	97.4-97.2	79	...	-19.8%
9:31	72	97.2-97.2	79	...	-33.6%
9:59	Current on 2000 M.A.	
9:59	84	97.2-97.3	79	...	-31.1%
10:06	84	97.3-97.4	79	...	-33.9%
10:12	Current off	
10:33	76	97.3-97.4	80	...	-32.7%
10:38	76	97.4-97.3	80	...	-32.7%
11:12	Current on	
11:12	80	97.2-97.3	82	...	-23.5%
11:18	80	97.3-97.6	82	...	-27.6%
11:26	Current off	
11:55	72	97.6-97.6	84	...	-23.8%
12:02	Sparksgaps opened wide—2400 M.A.	
12:02	80	97.6-98.2	84	Slight diaphoresis	-25.3%

In Charts IV, A and B are shown the metabolic curves obtained on patient F. K. as body temperature was rising and falling in fever induced by the following five methods: 1, Diathermy current; 2, electric cabinet and hot moist air; 3, a method combining 1 and 2; 4, electric blanket; 5, typhoid vaccine.

TABLE 2.—THE PERCENTAGE RISE OF METABOLIC RATE FOR EACH DEGREE RISE OF TEMPERATURE IN DIFFERENT FORMS OF THERAPEUTIC FEVER.

Typhoid vaccine	9.3%
Electric blanket	7.9%
Diathermy, cabinet and hot moist air—Exp. I	7.7%
Exp. II	7.7%
Electric cabinet and hot moist air	6.9%
Diathermy—Exp. I	3.9%
Exp. II	2.4%

A rather striking parallelism is seen in all methods of fever induction except when diathermy current alone is used. (The marked increase in metabolic rate in this patient during the typhoid vaccine chill, plus 170%, is not included.) The average increase in metabolic rate for each degree of temperature rise (Table 2) varied from 2.4% and 3.9% for fever induced by diathermy current alone to 9.3% for typhoid vaccine fever. The results obtained in these different methods of fever induction agree quite well with the accepted rise of 7.2% for each degree of body fever¹⁴ except for diathermy current alone. The small increase in the latter type of fever may be due (a) to the absence of any protein destruction in fever induced by diathermy alone and (b) to the absence of the hot moist air blanket.

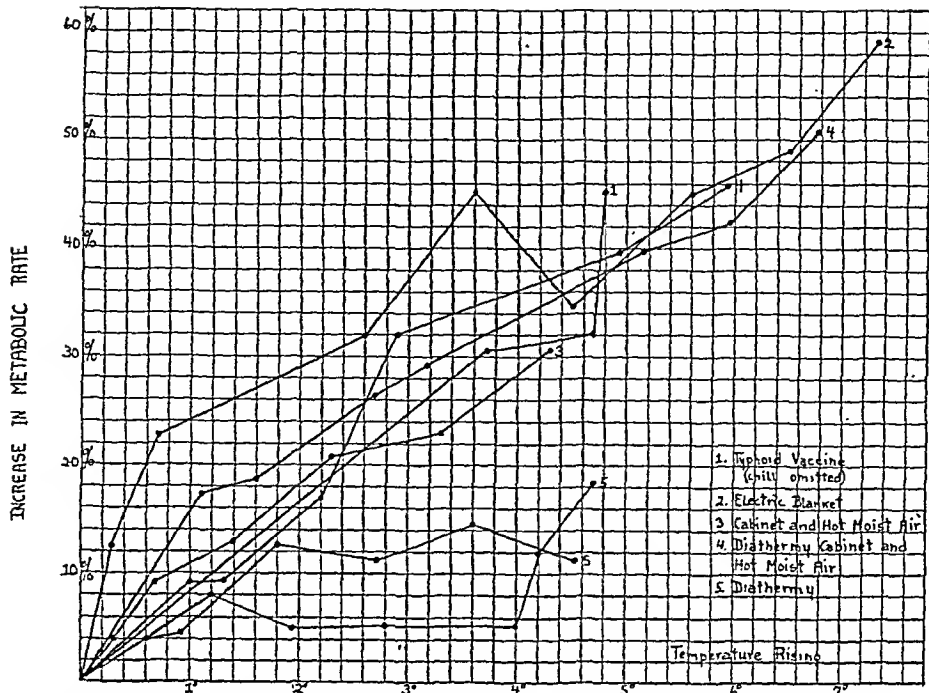


CHART IV A.—Comparison of metabolic rates in different modes of therapeutic fever.

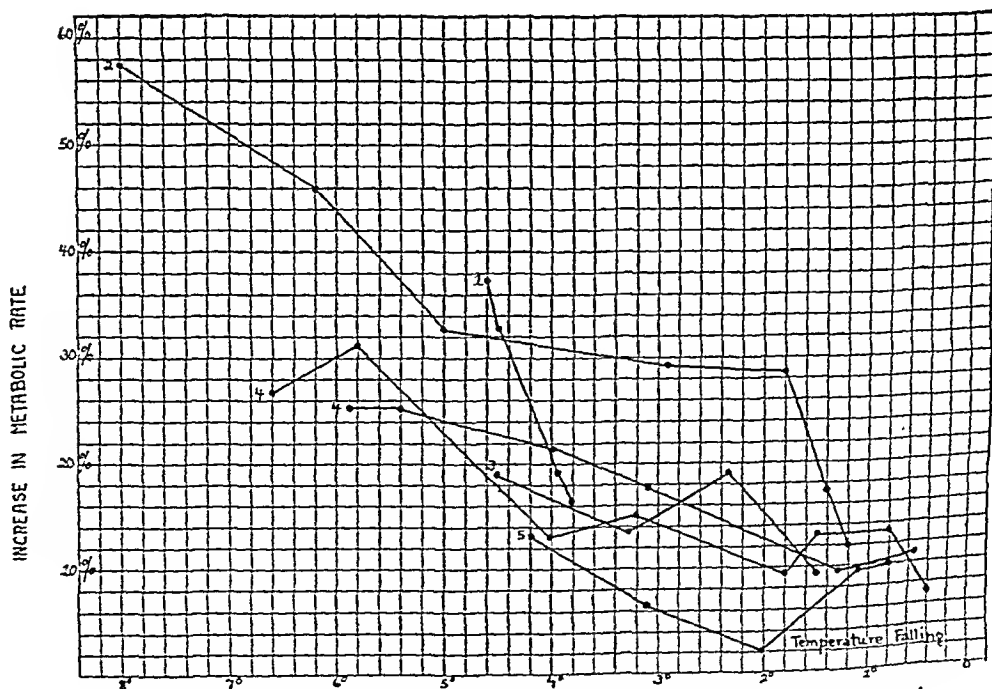


CHART IV B.—Comparison of metabolic rates in different modes of therapeutic fever. (See Chart IV A.)

The rapidity of body temperature rise did not appear to play any part in the results obtained in these five different methods (Table 3), contrary to the belief of some that higher metabolic rates are obtained in acute fevers than in chronic ones.^{10,11} Nasset and co-workers⁷ felt that the rate of increase in body temperature was an important factor in the high metabolism results obtained by them on dogs in whom body temperature was raised by diathermy. Fever induction in patient F. K. by means of diathermy current combined with the electric cabinet and hot moist air required an average of 11 minutes for each degree of body temperature rise. In fever induced by the electric cabinet and hot moist air, an average of 63 minutes was required for each degree of temperature rise. In spite of this marked difference in time interval the increase in metabolic rate for each degree of body temperature in both instances was about the same, 7.7% and 6.9% respectively (Table 2).

TABLE 3.—A COMPARISON OF THE RATE OF RISE OF BODY TEMPERATURE IN THERAPEUTIC FEVER.

	Temperature Range.	Minutes per degree rise.
Diathermy, cabinet and hot moist air	99.5-105.7	11
	98.2-105.3	11
Typhoid vaccine	99.0-103.8	30
Electric blanket	97.8-105.4	33
Diathermy current	99.2-104.0	35
	97.2-101.8	39
Electric cabinet and hot moist air	99.6-104.0	63

A rather rapid and fairly marked drop in the metabolic rate occurred when patient F. K. was uncovered and body temperature allowed to fall in fever induced by the cabinet and hot moist air, and by the combined method of cabinet, moist air and diathermy. A similar but less marked fall occurred in fever induced by the electric blanket and typhoid vaccine. In fever induced by diathermy current alone, the metabolic rate was approximately the same when body temperature was rising and falling. The drop in metabolic rate with uncovering of the patient was most marked in those methods in which hot, moist air was a factor in raising body temperature.

Summary. 1. Metabolic rates were determined on 7 patients with neurosyphilis in whom fever was induced by artificial means. In 6 patients in whom fever was induced by the combined method of diathermy current, electric cabinet and hot moist air, determinations were started about $2\frac{1}{2}$ hours after a light breakfast. In the seventh patient in whom fever was induced by 5 different methods: *a*, Diathermy current; *b*, electric cabinet and hot moist air; *c*, a method combining (*a*) and (*b*); *d*, electric blanket; *e*, mixed typhoid vaccine; all determinations were made under basal conditions.

2. An increase in the metabolic rate occurred when fever was induced by the combined method of diathermy current, electric light cabinet and hot moist air. Though a rather suggestive linear

relationship was present, fluctuations of a fairly marked degree occurred at different temperature levels when the group is taken as a whole. This may be due to individual variations in the degree of discomfort manifesting itself especially by hyperpnea, the metabolic rates at higher levels paralleling, as a rule, the amount of hyperpnea present.

Repeated metabolic rates obtained on 1 patient under basal conditions in a series of experiments during which body temperature was raised by similar methods and maintained at different levels from 1 to 3 hours revealed a fairly uniform increase in body metabolism for each degree of temperature rise.

3. The removal of the insulating hot, moist air blanket when body temperature had reached its desired height was followed in nearly all cases by a rather steep fall in metabolic rate, whether body temperature remained at the same level, fell or even rose.

4. Metabolic rates for similar temperature levels were higher when the temperature was rising than when falling.

5. Diathermy current *per se* over short time intervals had no specific effect upon the basal metabolic rate provided no rise in body temperature occurred. Alteration of the frequency of the diathermy current at increased temperature levels also caused no appreciable change in the metabolic rate.

6. The increases in metabolic rate obtained on the 1 patient in whom temperature rise was induced by the 5 different methods enumerated above showed a rather striking parallelism and did not differ much from the accepted rise of 7.2% for each degree Fahrenheit except in fever induced by diathermy current alone. In the latter the average rise in metabolic rate was 2.4% and 3.9% for each degree fever. The rapidity of rise in body temperature played no part in the results obtained.

7. Repeated fever treatment of 1 patient over a period of 7 months had no residual effect upon the basal metabolic rate.

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A STUDY OF THE COAGULATION DEFECT IN HEMOPHILIA AND IN JAUNDICE.*

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PROGRESS in the management of hemorrhage in hemophilia and in certain types of obstructive jaundice has been much impeded by the lack of a practical concept of blood clotting. A distinct need exists for a simple theory which may serve as a guide in the clinical study of disturbances in the clotting function of the blood. Recently Wöhlisch¹ in a thorough and critical review of the coagulation of blood, constructed a theory which incorporates the essential ideas of Bordet,² Morawitz,³ and others. According to this concept clotting proceeds in two phases:

I. Prothrombin + thromboplastin + calcium = thrombin

II. Fibrinogen + thrombin = fibrin

Thus, only 4 constituents are essential for clotting: prothrombin, thromboplastin, calcium, and fibrinogen. By the interaction of the

* This work was presented before the Twenty-ninth meeting of the American Society of Biologic Chemists at Detroit, April, 1935. It was supported by the Blossom Fund.

first three components, thrombin is formed, and this substance has the power to convert soluble fibrinogen into insoluble fibrin. If this simple concept of blood clotting is correct and sufficiently comprehensive, any disturbances in coagulation should be traceable to a qualitative or quantitative alteration in one of these essential components. In this study these 4 substances were carefully considered in an effort to find and to develop satisfactory methods for their estimation or quantitative determination. From a review of the literature, it became apparent that fibrinogen and calcium were probably rarely responsible for disturbances in blood clotting and therefore required little consideration other than a brief summary of their relation to clotting.

Fibrinogen. The concentration of fibrinogen in plasma varies normally from 0.3 to 0.75%, but this wide range has no demonstrable effect on clotting time. We have even found that adding purified fibrinogen to plasma does not alter the speed of clotting. It seems fairly certain that fibrinogen plays an entirely passive rôle, and that the rate of clotting depends primarily on the concentration of thrombin. Nevertheless, it is obvious that in the total absence of fibrinogen, no clotting can occur, and interestingly, 2 such cases have been reported in which fatal hemorrhage had to be attributed to a lack of fibrinogen in the blood.^{4,5} This condition Wöhlisch¹ has named pseudohemophilia. It can be reproduced in animals as illustrated by the following experiment:

A freshly prepared and filtered saline extract of rabbit brain (20 cc.) was injected intravenously into a dog. A severe reaction occurred immediately, respirations became shallow, and a nystagmus developed. The fibrinogen which was 0.44% before the injection dropped to 0.09 in 5 minutes and to a mere trace 30 minutes after the injection. The dog was killed 1 hour later and autopsied. No definite intravascular clotting could be found, but there was a relatively small pulmonary infarct and also a small mesenteric infarct.

While fibrinogen does not influence the clotting time, it is conceivable that if its concentration is too low, a fragile and poorly adhering clot will form. In hemophilia, however, a normal fibrinogen concentration has been found by all investigators.^{6,7,8} In obstructive jaundice the literature is more conflicting. The work of Doyon,⁹ Whipple and Hurwitz¹⁰ Foster and Whipple¹¹ and others show that liver damage can markedly reduce the blood fibrinogen. Recently, however, Linton¹² studied a series of obstructive jaundice cases, and found an elevation of fibrinogen even in those patients that died from hemorrhage. We have obtained essentially similar results. It seems fairly improbable, therefore, that fibrinogen deficiency can be the causative factor for the hemorrhagic diathesis.

Calcium. Contrary to the widely accepted view that ionized calcium of the blood influences the rate of clotting, it seems more

likely that it is only the organically combined calcium which is directly essential for the formation of thrombin. Scott and Chamberlain¹³ have demonstrated that the quantitative removal of ionized blood calcium with oxalate will not prevent clotting; and they as well as Vines,¹⁴ and Steward and Percival¹⁵ have found that it requires 3 times the theoretical amount of oxalate before clotting is completely inhibited, which suggests that the organically bound calcium must be precipitated before the clotting process is stopped. Eagle¹⁶ in a recent paper discussed the possibilities that thrombin may be a calcium-containing compound. Since these same considerations may be applied to prothrombin, it is likewise conceivable that in the latter, calcium may be an essential part of the molecule and that therefore in the conversion of prothrombin to thrombin, inorganic calcium perhaps plays no direct rôle. Ionized calcium is however a dominant factor in platelet lysis, as Ferguson¹⁷ has convincingly demonstrated in a recent work, thus confirming the observations of the older investigators. The question why calcium only becomes effective in shed blood still remains unanswered. It is doubtful whether clinically even marked changes in the concentration of inorganic blood calcium have any significant influence on the clotting time. No hemorrhagic diathesis has been observed in the extreme hypocalcemia of parathyroid deficiency, nor has intravascular clotting been reported in cases of hyperparathyroidism in which hypercalcemia of long duration often was present. Experimentally, Ravdin, Riegel, and Morrison¹⁸ could demonstrate no change in the coagulation time of blood after inducing a hypocalcemia in dogs by parathyroidectomy, nor by bringing about an elevation of blood calcium with parathormone. In hemophilia the concentration of calcium in blood is normal,^{19,20,21} and in obstructive jaundice, even in severe hemorrhagic cases, no significant change in blood calcium is found. Wangensteen²² who has carefully reviewed the literature concluded that a deficiency of calcium has not been adequately demonstrated in any hemorrhagic disease. Ravdin and his coworkers were unable to reduce the clotting time of normal and of jaundiced dogs by intravenous calcium injections. It is probable that any beneficial effect obtained by calcium administration may be due to its therapeutic action on liver function rather than on any direct influence on clotting.

Since neither fibrinogen nor calcium seem to be important factors in the hemorrhage seen in hemophilia or obstructive jaundice, attention must be centered on prothrombin and thromboplastin. Unfortunately no generally accepted methods for studying these two agents are available; in fact, even their nature is still a subject of controversy. The first task that had to be undertaken was the development of a method for estimating prothrombin, and the second, the preparation of a stable and active thromboplastin.

The method developed for the estimation of prothrombin depends

on the conversion of this substance to thrombin, and determining the activity of the latter in terms of clotting time, since the speed of clotting is a function of the concentration of thrombin. From the equation:

Prothrombin + thromboplastin + calcium = thrombin
it can be postulated that if both calcium and thromboplastin be kept constant, the rate of thrombin formation becomes proportional to the concentration of prothrombin. Incidentally, Eagle²³ has demonstrated that the amount of thrombin formed is independent of calcium and platelets but varies directly with the plasma factor (prothrombin). By employing oxalated plasma and recalcifying with a fixed and optimal quantity of calcium, this factor is made constant. On adding an active preparation of thromboplastin, a maximum acceleration in coagulation time is obtained even with an exceedingly small amount, and, significantly, further addition will not shorten the clotting time, as shown by Table 1. Thus, with the addition of a fixed quantity of calcium and an excess of thromboplastin, prothrombin is the only variable and the clotting time of oxalated plasma under these conditions can be considered a direct measure of the prothrombin concentration of the blood. On this basis the following test was developed.

TABLE 1.—THE PRODUCTION OF A CONSTANT MINIMUM CLOTTING TIME BY THE ADDITION OF THROMBOPLASTIN TO PLASMA.

Thromboplastin* added cc.	0.00†	0.002	0.01	0.02	0.05	0.10	0.20
Clotting time	sec. 110	40	22	22	22	22	22

Prothrombin Determination. Nine cubic centimeters of blood, withdrawn rapidly and with special precaution to avoid trauma, are promptly and thoroughly mixed with 1 cc. of M/10 sodium oxalate, and centrifuged at a low speed for 5 minutes. Of this plasma 0.1 cc. is transferred to a dry clean test tube (13 by 100 mm.), and mixed with 0.1 cc. of thromboplastin solution. Then, 0.1 cc. of M/40 calcium chlorid is added, and the tube quickly shaken, and placed in a water bath kept at 37° C. The exact time required for the formation of a solid clot is recorded. With an active preparation of thromboplastin, as will be described, normal human plasma will clot consistently in 22 to 25 seconds.‡

If the assumption is correct that the clotting time is dependent on the prothrombin concentration, any dilution of plasma should produce a delay in the coagulation rate. This actually occurs as

* 10% aqueous emulsion of rabbit brain heated to 60° C.

† Mixed with 0.1 cc. human plasma, and 0.1 cc. M/40 calcium chlorid.

‡ A thromboplastin of this degree of activity was consistently obtained using a series of more than 20 rabbits secured in New York City. Thromboplastin prepared from rabbits now obtained in Milwaukee has an equally consistent but distinctly great activity. It will clot human plasma in 16 to 17 seconds and that of rabbits and dogs in 7 to 9 seconds. This finding does not, however, alter the correctness or significance of the results presented in this paper.

is seen in Table 2. In spite of the excess thromboplastin, the clotting time increases as the plasma is diluted, so that when the prothrombin has been reduced to $\frac{1}{5}$ of normal, the clotting time is increased to 65 seconds. In order to guard against the possibility that the prolonged clotting is due to dilution of some other constituent in the plasma, dilutions were made with both normal saline solution and with plasma that had been treated with aluminum hydroxid. This reagent removes or inactivates prothrombin without apparently causing any other demonstrable change.²⁴ Thus, a plasma treated with sufficient aluminum hydroxid can be considered as a prothrombin-free plasma. Since the results with either diluent are the same, it seems reasonable to conclude that the decrease in prothrombin concentration alone is responsible for the prolonged clotting time. Interestingly, while undiluted human plasma on recalcification clots in 22 to 25 seconds when excess thromboplastin is present, rabbit's plasma under these conditions will clot in 12 seconds and dog's in 10 seconds. This indicates that the concentration of prothrombin in the blood of these two animals is much higher than in the human. When 1 part of rabbit plasma is mixed with either 8 parts of normal saline or with prothrombin-free plasma (treated with aluminum hydroxid), the resulting mixture will in the presence of added thromboplastin clot in 25 seconds. Since undiluted human plasma will clot in that time, it suggests that rabbit plasma contains about 9 times as much prothrombin as that of man.

TABLE 2.—PROGRESSIVE DILUTION OF PLASMA AS A MEANS OF DEMONSTRATING THE EFFECT DIMINISHING CONCENTRATIONS OF PROTHROMBIN HAS ON CLOTTING TIME.

Normal plasma cc.	Saline solution cc.	Clotting time* seconds.	Clotting time with excess thromboplastin† seconds.	Normal plasma cc.	Prothrombin-free plasma‡ cc.	Clotting time* seconds.	Clotting time with excess thromboplastin† seconds.
0.5	0.0	120	23	0.5	0.0	120	23
0.4	0.1	110	30	0.4	0.1	115	31
0.3	0.2	115	35	0.3	0.2	115	35
0.2	0.3	115	45	0.2	0.3	130	45
0.1	0.4	150	65	0.1	0.4	150	65

* By the unmodified method for determining the clotting time of recalcified plasma.

† By the new prothrombin method.

‡ Plasma treated with aluminum hydroxid.

Determination of the Clotting Time of Recalcified Plasma. By omitting the addition of excess thromboplastin, but otherwise following the directions of the method outlined for the determination of prothrombin, one determines the clotting time of recalcified plasma, which for normal plasma is from 90 to 130 seconds. This method is still commonly called Howell's Prothrombin Time. The term, however, is unfortunate since this method apparently does not determine prothrombin; in fact, the thromboplastin derived principally from the platelets is an even more important factor influencing the clotting time than is the prothrombin. This can

readily be demonstrated, for on centrifuging oxalated plasma at a high speed, its clotting time on recalcification may become 3 times as long as that of the same plasma centrifuged at such a speed that practically no platelets are removed. Nygaard²⁵ observed that within limits the clotting time runs roughly inversely proportional to the number of platelets remaining in the plasma. Thus, the mechanical removal of the platelets is sufficient to alter profoundly the clotting time, although there is obviously no diminution of prothrombin, but only of thromboplastin. Moreover, by diluting plasma with saline solution or prothrombin-free plasma, no significant change in clotting time occurs until the prothrombin is reduced to nearly $\frac{1}{5}$ of normal, this demonstrating that the method is altogether useless for estimating prothrombin, in contrast to the new prothrombin test which responds promptly even to a relatively small diminution of prothrombin. Nevertheless, the older method is clinically valuable. The prolonged clotting time of recalcified hemophilic plasma which was first observed by Howell²⁶ has been repeatedly confirmed. The application of the test to cases of jaundice for the detection of a hemorrhagic diathesis was found successful by Bancroft, Kugelmass, and Stanley-Brown,²⁷ Lewisohn,²⁸ and Nygaard.²⁹ Bancroft and Stanley-Brown^{27, 30} have further observed that a threatening impending postoperative thrombosis may be indicated by an abnormal shortening of the clotting time.

Preparation and Properties of Thromboplastin. For carrying out the new prothrombin test successfully, it is necessary to prepare an active and stable thromboplastin. Rabbit brain was found to be the most satisfactory source, since it is not only very active, but it can be preserved in the dry state for weeks with little deterioration in activity. The preparation is as follows: the brain of a freshly killed rabbit is freed of the larger superficial bloodvessels, washed, then ground to a paste, and spread in a thin layer on a plate glass, or a flat dish. After thoroughly drying at 37° C., the material is removed from the plate, and preserved in a stoppered container. By mixing 0.2 gm. of this material with 0.3 cc. of 0.85% sodium chlorid, and incubating for 15 minutes, an emulsion is obtained which has practically maximum activity, *i. e.*, it will when added to human plasma cause clotting in 22 to 25 seconds. Any preparation which fails to show this activity is discarded. A fresh emulsion prepared from rabbit brain, thymus, or lung, and heated to 60° C. for 15 minutes to inactivate any prothrombin which may be present, likewise brings about clotting in 22 seconds, thus suggesting that the thromboplastin in these 3 tissues is identical. For the test either the fresh or the dry preparation may be employed. Attempts to purify or isolate the active constituent invariably led to a diminution of activity, and since the product contains no impurity which would interfere with the present problem no further attempts at purification were deemed necessary.

Thromboplastin appears to be, as Howell and Cekada³¹ suggested, a cephalin-protein compound. It is not, as is often stated, free cephalin. In the absence of prothrombin, it will not clot fibrinogen. The aqueous emulsion when extracted either with ether or petroleum ether loses no activity, nor is any thromboplastic activity found in the ether extract. The dry preparation, however, is totally inactivated when extracted with these immiscible solvents, and the extract will be weakly active in accelerating clotting.

Thromboplastin undoubtedly is an important factor that must be considered in the problem of the maintenance of the fluidity of intracorporal blood. Circulating blood contains fibrinogen, calcium, prothrombin, and platelets, but no free thromboplastin as long as the platelets remain intact. Even if a small amount of thromboplastin were liberated and a corresponding amount of thrombin formed, clotting would not occur immediately, for it requires even 4 to 5 minutes for blood to clot in a test tube. Clotting is dependent upon the concentration of thrombin, and in circulating blood, any thrombin formed is under normal conditions diluted sufficiently to be ineffective in forming a clot.³² As a further protection to the individual, any formed thrombin is normally removed at a rate which prevents a dangerous accumulation. It is, therefore, unnecessary to postulate the existence of any antithrombin or antiprothrombin to explain the fluidity of blood. The fact that thrombin must reach a certain concentration before clotting can take place is sufficient protection against intravascular clotting, provided no general or localized circulatory disturbances are present. It seems certain that the disintegration of platelets is necessary for clotting, and that an important factor in this process is contact with roughened surface. The smooth endothelial lining of the vascular system plays an important function in keeping blood fluid. A roughened or calcified intima may produce clumping and lysis of platelets that may give rise to clotting. The laying down of fibrin in an aneurysm sac can readily be explained. The rough surface favors platelet lysis and the local eddies and stagnation of the blood allows sufficient thrombin to accumulate to cause clotting in the aneurysm sac without extension into the normal lumen. In external hemorrhage, clotting occurs because not only does the roughened surface favor platelet lysis, but also because additional thromboplastin is available from the injured tissue. Is it not possible that the rich content of thromboplastin in such tissues as brain and lung is a useful factor in guarding against extensive hemorrhage in organs where even moderate bleeding is serious, and further that the presence of thromboplastin in saliva plays a useful rôle when the wounded animal licks its wound?

Hemophilia. In studying the plasma of 6 hemophilia patients with the new test for prothrombin, normal results as regards quantity of this constituent were obtained in every case. No matter

how much the clotting time was prolonged, hemophilic plasma after the addition of excess thromboplastin clotted normally, *i. e.*, in 22 to 24 seconds (Table 3). Similar results were obtained using whole blood and employing the technique of the Lee White method with the modification that in one tube 0.1 cc. of thromboplastin was added. The results recorded in Table 4 show that even when the clotting time was 10 times longer than normal it became the same as that of ordinary blood when thromboplastin was added.

TABLE 3.—THE EFFECT OF THROMBOPLASTIN ON THE CLOTTING TIME OF HEMOPHILIC PLASMA.

	Clotting time* seconds.	Clotting time with excess thromboplastin seconds.
Normal	110	22
Case I	330	22
Case II	260	23
Case III	405	22
Case IV	210	22
Case V	270	24
Case VI	205	22

* Of recalcified plasma.

From these results it can be concluded that hemophilic blood contains a normal concentration of prothrombin. The question remains, however, whether the defect of hemophilic blood lies in a qualitative peculiarity of the prothrombin, as Addis⁶ postulated, which makes it resistant to activation, but which can be overcome by excess thromboplastin; or whether there is a deficiency in thromboplastin. As normal plasma can be made to clot normally with hemophilic platelets, a possible prothrombin defect must be kept under consideration. An abnormal stability of the platelets against lysis or a diminished prothrombin content could cause a thrombo-

TABLE 4.—THE CLOTTING TIME OF WHOLE BLOOD IN HEMOPHILIA. THE EFFECT OF THROMBOPLASTIN.

Subject.	Lee White method.	
	Unmodified seconds.	With added thrombo- plastin* seconds.
Normal	210	30
Hemophilia Case I	1260	45
Hemophilia Case II	2260	24

* 0.1 cc. thromboplastin emulsion added to 1 cc. of blood.

plastin deficiency. The work of Sahli,⁷ Wöhlisch,³³ Minot and Lee,³⁴ and others support the hypothesis that the platelets of a hemophilic patient are less active than those of a healthy individual. Fonio³⁵ once held the view that the hemophilic platelets contain less thrombocyme (thromboplastin), but recently³⁶ has concluded that the stability of the platelets is responsible for hemophilia. Howell and Cekada³¹ also attribute the delayed clotting to a slow disintegration of platelets. Interestingly, the tissues other than platelets

of a hemophilia patient appear unquestionably normal in regard to their thromboplastin content. Minot and Lee,³⁴ and Lowenberg and Rubenstone³⁷ found that the organs of a hemophilic patient had the same content of thromboplastin as those of a normal individual. The saliva of one of our hemophilia cases had a very active thromboplastic action; 0.1 cc. of his saliva clotted recalcified human plasma in 22 seconds, whereas the saliva of normal individuals often only produced clotting in 50 seconds.

The treatment of hemophilia is still very unsatisfactory. While it is clear that an excess of thromboplastin makes hemophilic blood clot normally, no method is known for supplying this substance except locally. There is no way to increase the thromboplastin content of platelets or to alter their stability. Blood transfusion remains the most reliable therapeutic measure for combating hemorrhage, and Minot and Lee³⁴ found that after a transfusion, the clotting time of a hemophilic became normal for a few days. Nevertheless, it is often found that hemorrhage persists after transfusion. This can probably be explained as follows. The amount of available thromboplastin from platelet lysis even in normal blood is relatively small, and therefore it is difficult to supply sufficient blood to correct the defective hemophilic blood. The newer methods of treatment, such as sensitization to a foreign protein; administration of the follicular hormone, theelin, and injection of snake venom still require further study before their value can be estimated. Active thromboplastin can be effectively used in any hemorrhage which can be approached locally. Parenterally it is unsatisfactory and may even be dangerous. It is doubtful whether intramuscular injection has any demonstrable beneficial effect, and intravenous administration is distinctly hazardous. If the preparation is active, it may cause extensive intravascular clotting, or cause a sudden disappearance of the fibrinogen such as we produced in the dog.

Jaundice. In studying the plasma from various types of jaundiced patients by the new method for determining prothrombin, it was found that this component was often greatly diminished, as illustrated in Table 5. Instead of obtaining a normal clotting time of 22 to 25 seconds, a delay, which in 1 case was as long as 90 seconds, was obtained. Significantly, the clotting time of recalcified plasma without the addition of extra thromboplastin was only slightly prolonged, thus giving no intimation of the extent that prothrombin had been diminished. As already pointed out when discussing the results of Table 2, the prothrombin factor has a wide margin of safety, and the component can be greatly diluted or diminished before a marked delay in clotting time occurs. Nevertheless, it has been shown by Lewisohn,²⁸ Nygaard²⁹, and us, that the plasmas of patients that develop so-called cholemic hemorrhages show a prolonged clotting time on recalcification. The delay is not due to insufficient thromboplastin, for it is clear from the present

studies that excess thromboplastin does not restore the normal clotting rate as it does in hemophilic plasma. These findings therefore suggest that the hemorrhagic tendency in jaundice is brought about by a diminution of prothrombin. Further work is required, however, before this conclusion can be definitely established; nevertheless, it can be used as a working hypothesis both for theoretical and clinical studies. Thus, the beneficial results from blood transfusions, which are well recognized clinically, can be readily explained. Because of the wide margin of safety in the prothrombin concentration, which has already been emphasized, even a partial restoration of the prothrombin will bring about a sufficient shortening of the clotting time to bring it within normal range.

TABLE 5.—THE CLOTTING TIME OF PLASMA FROM JAUNDICED PATIENTS. THE EFFECTS OF ADDED THROMBOPLASTIN.

Diagnosis.	Clotting time* seconds.	Clotting time with added thromboplastin seconds.
Normal	110	23
Carcinoma of biliary tract	210	85
Stenosis of common duct	150	37
Chronic hepatitis and stenosis of common duct	140	90
Carcinoma of head of pancreas	150	50
Liver abscess	120	35

* Of recalcified plasma.

Summary. On the basis that the rate of clotting is proportional to the concentration of thrombin, and that this agent is formed by the interaction of prothrombin, thromboplastin, and calcium, a new method for estimating prothrombin has been developed. By employing oxalated plasma, recalcifying with an optimal amount of calcium, and adding an excess of thromboplastin, prothrombin become the only variable in the reaction and the amount of thrombin formed depends on the concentration of prothrombin. The clotting time, therefore, becomes a direct measure of the prothrombin.

By means of this new test it has been found that the prothrombin concentration in the blood of normal individuals is remarkably constant, but much lower than in dog's and rabbit's blood.

In hemophilia the prothrombin was found normal in quantity, *i. e.*, the clotting time of hemophilia plasma clotted in the same time as normal plasma, when excess thromboplastin was added. In the plasma of various types of jaundice a delayed clotting rate in the presence of excess thromboplastin was obtained, suggesting that the hemorrhagic tendency in jaundice is caused by a diminution of prothrombin.

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- (Titles have been omitted for sake of brevity.)

GAUCHER'S DISEASE OF LATE ONSET WITH KIDNEY INVOLVEMENT AND HUGE SPLEEN.*

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CASE reports and discussion of Gaucher's disease have occupied a fairly prominent position in the literature during recent years. The total number of cases reported is not large, however, and it seems worth while to record this case, particularly since it showed several unusual features.

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Case Report. History. A white farmer, aged 47, was admitted to the Sheltering Arms Hospital on May 18, 1934, complaining of a large mass in the abdomen and aching in both legs. There was no history of any familial diseases. His mother died of pneumonia and father of kidney disease. All of his 4 brothers and sisters are living and well. His wife died of puerperal sepsis, leaving 5 healthy children. The patient was in excellent health prior to his present illness. He had the usual diseases of childhood, but no other definite illnesses that he could remember. Jaundice and any symptoms of malaria or venereal diseases were specifically denied. Since the patient was born in the southwestern part of Virginia and had lived there all his life, the possibility of having contracted any tropical diseases seemed remote. He is not known to have had any Jewish ancestry.

The present illness started about 12 years ago when the patient noticed enlargement of the abdomen. He was then examined by Dr. E. M. Corns, of Kingsport, Tennessee, who found an enlarged spleen. The enlargement of the abdomen at that time had come on gradually during the preceding 4 months. This was accompanied by loss of several pounds in weight, weakness, and the development of a copper color in the skin. The loss in weight and the weakness were attributed to repeated hemorrhages from the intestinal tract which had occurred over a period of 2 months. From 1 to 5 times a day he would pass from a pint to a quart of bloody, "flesh-like" stools. After this illness of 2 months he rapidly gained in strength and weight. There was no further bleeding from the gastro-intestinal tract, and no hemoptysis or hematuria. Repeated hemorrhages beneath the skin and mucous membranes started 7 years after the enlargement of the abdomen was first noticed and during the last 5 years of his illness progressively increased in frequency and severity, especially in cold weather. Mild epistaxis occurred frequently throughout the 12 years of his present illness. The aching in both legs began about 5 years before admission and was accompanied by swelling and discoloration, particularly in the right lower extremity, and most markedly about the right thigh and knee. These symptoms would appear with cold weather, usually in the month of December, and would clear up as soon as the weather became warm, so that the patient was able to return to his usual duties on the farm. Three years before admission he complained of severe pain in his right knee and was sent to a hospital to have his spleen removed for Banti's disease. His physician stated that there was no swelling or other signs of injury or abnormality in the knee, but the pain was so severe that the patient had to be given morphin hypodermically for relief. He left against advice soon after admission and before any examinations had been made. The pain in the knee lasted for about 3 weeks and did not return with the same severity. He worked until December, 1933, but from that time to his admission he became steadily weaker, and the discomfort, swelling, etc., in both lower extremities became progressively worse. There was only slight variation in the enlargement of the abdomen during the last 12 years, except that a few months before admission it markedly increased. No mental changes of any consequence were noted until a few months before admission when the patient became sluggish and extremely depressed over his condition.

Treatment previous to admission to the hospital was merely symptomatic and palliative.

Physical Examination. The patient was rather poorly nourished and decidedly emaciated. He seemed to be quite ill. The skin was pale and showed slight jaundice, multiple petechiæ and several large subcutaneous hemorrhages. The typical yellow wedge-shaped pingueculæ were present in both scleræ. The pupils reacted sluggishly. The gums were swollen and hyperemic and bled easily. The lungs were essentially normal. Except for a soft systolic murmur over the tricuspid area, examination of the heart

was entirely negative. The blood pressure was 110 systolic and 85 diastolic. There was a mass in the abdomen which extended from above the costal border down into the pelvis, occupying the entire left side of the abdomen and extending about 2 to 3 cm. to the right of the midline. A definite notch could be palpated on the medial side of this tumor. The liver was palpable 2 to 3 cm. below the costal border. There was no abdominal tenderness and no demonstrable ascites. Both legs showed a brownish pigmentation. The right leg and thigh were edematous, and the right knee showed a firm diffuse swelling which was quite tender, probably caused by a hemorrhage into the joint capsule.

Laboratory Examinations. On admission, the hemoglobin was 42%; red blood count, 2,750,000; white blood count, 2300; neutrophils, 83%; lymphocytes, 12%; large mononuclears, 2%; eosinophils, 2%; basophils, 1%. Urinalyses were essentially negative. Subsequent examinations of the blood showed a progressive anemia and leukopenia. The blood Wassermann reaction was negative.

Treatment and Course. The patient's condition grew steadily worse from the time of admission. Temperature ranged between 96° and 99° F. Liver extract and iron had no effect on his anemia. Calcium gluconate given intravenously seemed to lessen the tendency to bleeding and relieved temporarily the pain in the knee. Later large doses of morphin were necessary to control the pain. During the last few days before death, he was irrational and confused. On June 11 (24 days after admission), he developed signs of pulmonary edema and died in a few hours.

Autopsy (Dr. Kinloch Nelson, 7 hours after death, the body having previously been embalmed). The appearance was that of a very emaciated, middle-aged, white man. Palpation of the abdomen revealed a large smooth mass extending from under the costal margin down to the left iliac crest and about 3 cm. to the right of the mid-line.

The pleural surfaces were smooth and glistening; lungs unusually pale except for hypostatic congestion of both bases posteriorly. On section much edematous fluid escaped. The pericardium was smooth and glistening with increased subepicardial fat and moderate coronary sclerosis. The myocardium and valves were grossly normal except the cusps of the aortic valve which were thickened and hardened, resulting in the amalgamation of two cusps in a hard, partially calcified mass. Aorta appeared normal.

The peritoneal surface was smooth and glistening, and contained about 500 cc. of clear thin yellowish fluid. The spleen was enormously enlarged, weighing 5890 gm. It measured 38 by 20 by 13 cm. and completely filled the entire left side of the abdominal cavity. Its surface was smooth, deep blue in color, with white spots irregularly scattered over it, and near the hilum a large white or pale yellow, soft area, about the size of an orange. On section the splenic substance appeared dark red or bluish, and firm. The pale area near the hilum on section was entirely composed of a whitish-yellow and apparently fatty substance. The splenic vessels were much enlarged and tortuous. The liver was large, dark brown, irregular and firm, and had the appearance of cirrhosis. The stomach, duodenum, small and large intestines were grossly normal. The appendix was represented by a short stump of atrophic sclerotic tissue. The pancreas was small but grossly normal. Both kidneys were somewhat enlarged, capsules stripped readily leaving a finely granular surface and were grossly normal on section. Ureters, bladder and prostate were normal.

MICROSCOPIC EXAMINATION (Dr. F. L. Apperly). Spleen shows the typical picture of Gaucher's disease, but in a most advanced stage. Practically the entire field is occupied by Gaucher cells, with large round pale cytoplasm and small darkly staining round or oval nucleus eccentrically placed. The cytoplasm appears to contain a fine network of fibrils. These



FIG. 1.—Photomicrograph of liver ($\times 130$) with masses of Gaucher cells lying between liver lobules and in places apparently invading the sinusoids. Liver parenchyma somewhat degenerated.



FIG. 2.—Photomicrograph of spleen ($\times 120$) with large pale Gaucher cells crowded into alveoli. Two areas show cells containing a considerable amount of hemosiderin pigment. A few cells of spleen pulp lie between the Gaucher masses.

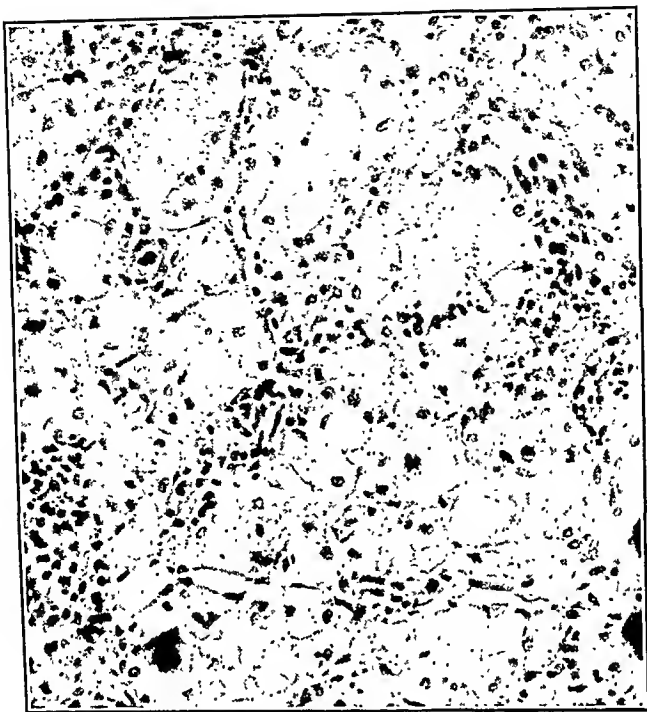


FIG. 3.—Photomicrograph of spleen ($\times 260$), same field as Fig. 2, with characteristic Gaucher cells, large and round, with very pale cytoplasm and small, round or oval, eccentric nucleus. Cells often crowded into alveoli.



FIG. 4.—Photomicrograph of kidney ($\times 75$) section from one area showing (in center) a group of large pale cells (Gaucher cells?) crowded into an alveolus. Note also cystic dilatation of many kidney tubules containing a coagulum.

cells seem crowded into distended spaces, in some of which are broken-down cells and dark pigment, extracellular and intracellular. The normal splenic substance is almost crowded out of existence (Figs. 2 and 3). The white necrosed area consists of a Gaucher cell complex, now quite necrosed, in which the general structure typical of a Gaucher's spleen is readily made out in ghostly outline. Stain for iron by potassium ferrocyanid shows that in the spleen Gaucher cells stain pale blue, but in the liver there are large areas in which these cells are completely unaffected, while in others only a faint blue color is observed. Contrasting with Pick's descriptions, there is no iron stain in the splenic trabeculae or endothelial cells of venous sinuses. With scarlet red, which shows bright red in the presence of true fats, and a paler different tint in the case of cholesterol—esters and cholesterol—fatty acid mixtures, the Gaucher cells stain a pale orange, which we may take as indicating the presence of cholesterol bodies in small amount. This is very noticeably more marked in the splenic necrotic area, especially under the capsule, than in other parts of the spleen (Table 1).

TABLE 1.

Analyst.	Cholesterol per cent dry weight.			Ether insoluble-alcohol soluble material, per cent dry weight.		
	Normal spleen.	Gaucher cells.	Degenerated areas.	Normal spleen.	Gaucher cells.	Degenerated areas.
The Authors	1.7	1.8	3.9	9.8	26.0	14.7
Bloom and Kern	2.4	2.6	...	17.6	22.4	...
Lieb	13.1*	35.0*	...

* Calculated on dry weight of ether extracted material.

Liver substance is shot through with areas of Gaucher cells lying along the interlobular borders but with some invasion along the sinusoids of the lobules, and apparently causing obstruction and parenchymal atrophy (Fig. 1).

Kidney sections show glomerular hyperemia, and tubular degeneration mainly. In one section, however, there are large cystic spaces, resembling hugely dilated tubules almost filling the low-power field, and lined with a low flattened epithelium, embracing an eosinophil coagulum. The remainder of the section shows the changes found in ischemic nephritis. In one section, however, a small space is seen filled with cells indistinguishable from Gaucher cells. Gaucher cells in the kidney have heretofore never been reported (Figs. 4 and 5).

Pancreas shows a normal parenchyma, but irregularly sclerosed arteries, with patchy calcification.

Lung section show no significant changes.

Bone marrow from the sternum shows no Gaucher cells, but a normal marrow.

Chemical Analysis. Dr. J. C. Forbes, Associate Professor of Chemistry, has kindly made a chemical analysis of the spleen. Samples were taken from formalin-hardened material of (a) normal spleen (b) a typical Gaucher area, and (c) an area in the Gaucher spleen which microscopically was seen to be composed of necrosed Gaucher cells.

The material was finely cut up, dried at room temperature, and pulverized. It was then extracted in a Soxhlet apparatus, first with ether, then with alcohol. Cholesterol was determined colorimetrically in the residue after ether extraction. The alcohol extract was

evaporated to dryness and the residue weighed. This material has not been further purified. It is, however, undoubtedly high in cerebroside since it readily reduces Benedict's solution after hydrolysis with hydrochloric acid.



FIG. 5.—Photomicrograph of kidney ($\times 260$), same field as Fig. 4, showing details of group of Gaucher cells in kidney.

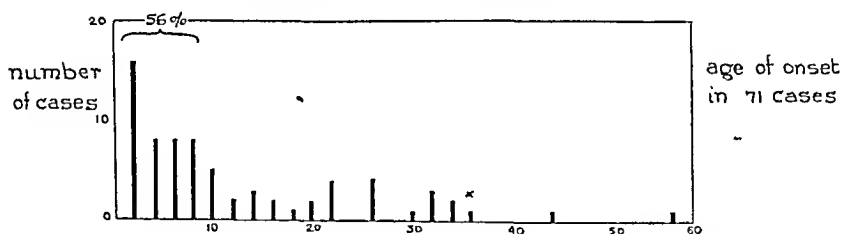


FIG. 6.—Graph constructed from 71 cases of Gaucher's disease, collected from the literature, showing the number of cases in each 2-year age period at which the disease was first noticed.

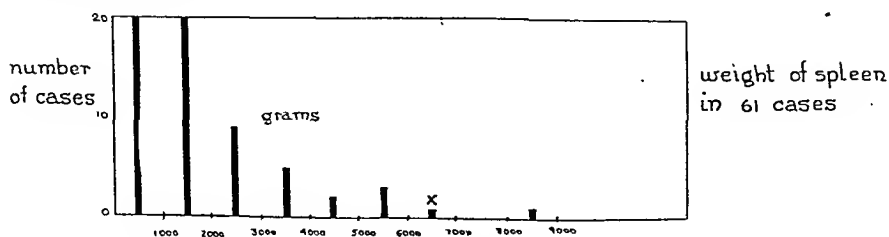


FIG. 7.—Graph constructed from 61 cases of Gaucher's disease in the literature showing the weight of the spleen where it is recorded.

In Table 1 our results are compared with those of Bloom and Kern,⁶ and of Lieb.⁷

A. Cholesterol. Our figures, and those of Bloom and Kern, show that there is no notable increase of cholesterol in the live lesions of Gaucher's disease, which is in keeping with the results found in our stained sections. In the necrotic area, however, the cholesterol content is doubled, possibly due to disintegration and partial absorption of cellular debris, the cholesterol remaining behind.

B. The ether-insoluble-alcohol-soluble fraction, which includes the cerebrosid, kersin, is increased to about 2 to 2½ times the normal, though in the degenerated necrotic areas it is increased to only a small extent above normal. It is possible that in these necrosed areas the lipoids are hydrolyzed into their constituents, some of which are readily absorbed.

Remarks. This case is remarkable for the following reasons: 1. The age of the patient. We have constructed a graph (Fig. 6) from 71 cases collected from the literature, showing the number of cases in each 2-year age period, at which the disease was first noticed. The graph shows that 56% of these cases appeared at or before the age of 8 years. Our patient was 35 when the disease was first noticed. Among these cases only 2 (aged 44 and 56) were older than our patient.

2. The size of the spleen. We have constructed another graph (Fig. 7) showing the weight of the spleen in 61 cases in the literature where this is recorded. Only twice has a spleen of greater mass than that of our patient been recorded. These spleens weighed 8100 gm. and 6250 gm. as against that of our case, with a weight of 5890 gm.

3. The appearance in the kidney of an area apparently composed of Gaucher cells. These cells, besides appearing in spleen, liver, bone marrow and lymphoid tissue, have occasionally been reported in the thymus, lungs and even cerebral cortex, but in no case have these cells been reported in the kidney.

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HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY.

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SINCE Mandl's¹ classical description of his case of hyperparathyroidism, the subject has appeared more and more frequently in the literature. To date, more than 100 carefully described cases have been reported. Of these, many have been successfully operated upon, and startling clinical improvement has been noted. The syndrome is so protean in its manifestations, and tends to simulate other medical conditions so closely, that it is frequently overlooked. This oversight is regrettable because therapy for hyperparathyroidism is so successful.

Albright² divided his group of cases into six types: 1, Classical hyperparathyroidism (von Recklinghausen's disease); 2, osteoporotic form of hyperparathyroidism; 3, hyperparathyroidism with nephrolithiasis; 4, acute parathyroid poisoning; 5, hyperparathyroidism simulating Paget's disease; 6, hyperparathyroidism with renal insufficiency (only 1 case of this type is presented in his series).

We present herewith a case of hyperparathyroidism with marked renal insufficiency. Removal of an adenoma of a parathyroid gland was followed by improvement.

Case Report. D. C., white, female, American, aged 44, a housewife, was admitted to this hospital July 3, 1934. For 1 month she had had numerous and varied complaints, chiefly pain in the legs radiating down from the knees, inability to stand, tenderness over the bones, pain on moving the joints with indefinite muscle pains, and a tumor of the left lower jaw (which was diagnosed as an epulis on biopsy). She complained also of frequency and nocturia, micturating almost every hour, with polyuria and a reversal of the day and night ratio, but at no time did she have any edema. There was marked anorexia, and a loss of 60 pounds in the past year, making her so weak that she lacked the strength to walk around. She was chronically constipated and frequently vomited food soon after meals. She also had dyspnea on slight exertion, precordial pain relieved by resting, and palpitation. Her mental state was one of constant anxiety, irritability and emotional instability. Her vision had been good, although her eyes showed chronic conjunctival congestion. She was absolutely definite in stating that her hearing was markedly impaired since all these peculiar things were happening to her.

Examination of the patient at the time of admission showed the temperature to be 100°, respiration 22, blood pressure 110/74. Physically, the patient showed only marked evidence of emaciation and loss of weight, and an epulis in the left mandible which was large, hard and smooth, reaching above the level of the biting edge of the teeth. There were arterio-

sclerotic changes in the eyegrounds, and both eardrums show calcification, more on the right side, where almost complete deafness existed. The muscles were flabby, with a marked decrease in muscle tone.

Laboratory Studies. The kidney function test showed an increased night specimen with specific gravity at 1.009 and below. The dye excretion was greatly decreased, being less than 5% after 2 hours. Roentgen rays of the chest and of the gastro-intestinal tract were negative. The blood sugar was 108.1 mgm.; urea nitrogen, 31.4 mgm.; creatinin, 2.5 mgm.; uric acid 4.3 mgm. The basal metabolic rate was +8. The blood Wassermann reaction was negative. The leukocyte count was 10,000 with 80% neutrophils, 18% lymphocytes, and 2% transitional cells; red blood count 4,540,000; hemoglobin 75% (Dare). The urine contained a very faint trace of albumin and 20 to 35 pus cells per high-power field with numerous bacteria. The electrocardiogram was normal. The weight was 114 pounds.

On high vitamin diet and supportive and symptomatic treatment, the patient improved somewhat and was discharged August 1, with the following diagnoses which, at the time, were felt to be unsatisfactory: chronic nephritis, epulis, menopause.

She was readmitted on September 10, with the story of having been bedridden since her discharge, and of having had an exacerbation of all the symptoms enumerated previously, which had subsided while in the hospital. On examination, the patient showed even more emaciation, marked cachexia, the epulis was greatly increased in size, and there was a generalized hemorrhagic eruption.

Laboratory Studies. The blood Wassermann reaction was negative; the leukocyte count was 9800 with 72% neutrophils, 26% lymphocytes, and 2% transitional cells; red blood count was 2,950,000; hemoglobin 60% (Dare). The urine showed 1+ albumin and pus cells too numerous to count, with many bacteria. The blood pressure was 110/74. The carbon dioxide combining power was 40%. The blood sugar was 95.2 mgm., urea nitrogen 58.8 mgm., uric acid 4.7 mgm., and creatinin 2.8 mgm. The weight was 90½ pounds. The kidney function test was essentially the same as on the first admission. The sedimentation time was 20 minutes, the bleeding time was 2 minutes, the coagulation time 5 minutes. The platelet count was 320,000 per c.mm. The Bence-Jones protein reaction was repeatedly negative.

No other physical or laboratory findings were obtained to aid in the diagnosis. At this time the general opinion was in favor of a systemic disease only secondarily affecting the kidneys, and the following possibilities were considered: avitaminosis, malignancy, kidney anomaly, calcium deficiency, malnutrition and starvation with mild acidosis. A blood calcium determination taken September 15th to rule out the diagnosis of avitaminosis and calcium deficiency disclosed a serum calcium of 19.5 mgm. per 100 cc. and a phosphorus of 6.8 mgm. This was confirmed on September 19th, when a serum calcium value of 19.6 mgm. was obtained. Thereupon, the diagnosis of hyperparathyroidism was made. Inclusive Roentgen ray pictures revealed no abnormalities in the long bones except somewhat increased trabeculation, and a small cyst in the third metacarpal bone of the left hand (Fig. 3). The skull plates showed osteoporosis and a ground-glass appearance with an accentuation of the inner table (Fig. 1). The ribs also showed definite osteoporotic changes. These findings bear out the statement of Camp³ that the predominant early changes in hyperparathyroidism occur in the flat bones. Roentgen ray of the jaw in the region of the epulis showed it to be an osteoclastic process (Fig. 2A), and the relationship between the epulis and the general condition was recognized, as was demonstrated by Albright.²

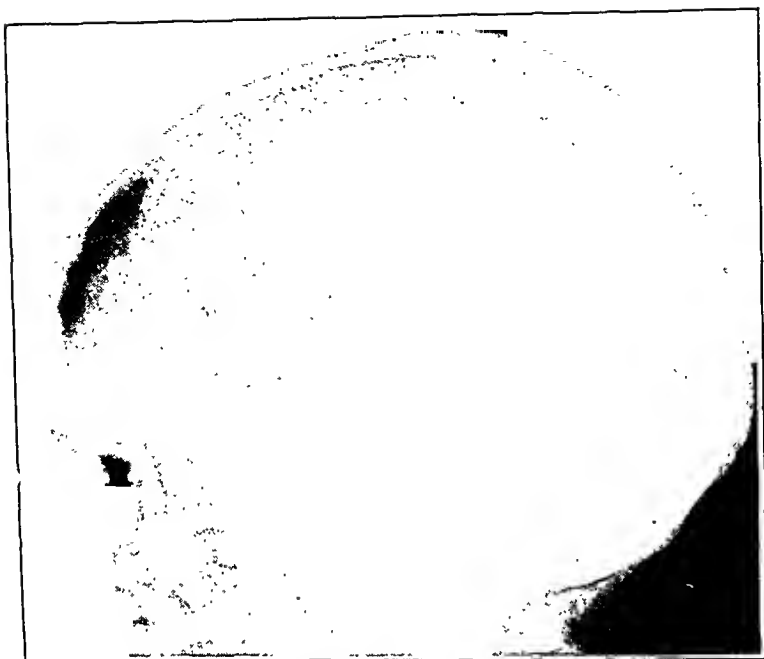


FIG. 1.—The bones of the calvarium show the characteristic changes of hyperparathyroidism, which are mild in this case. There is thickening of the skull in the frontal, parietal and occipital regions, with indistinctness of the inner and outer tables; and definite and marked osteoporosis of the skull, with the classical, granular, ground-glass appearance.



FIG. 2A.—Roentgen ray of the mandible (obliquely from below), the left ramus of which contained the epulis, shows a bone defect in the alveolar region with a sharply outlined contour and no periosteal reaction around it. The surrounding bone shows marked osteoporosis. This was taken pre-operatively.



FIG. 2B.—Four weeks after operation, fibroosteosis is marked, and the repair process is definitely shown in the left ramus of the mandible by new bone formation.

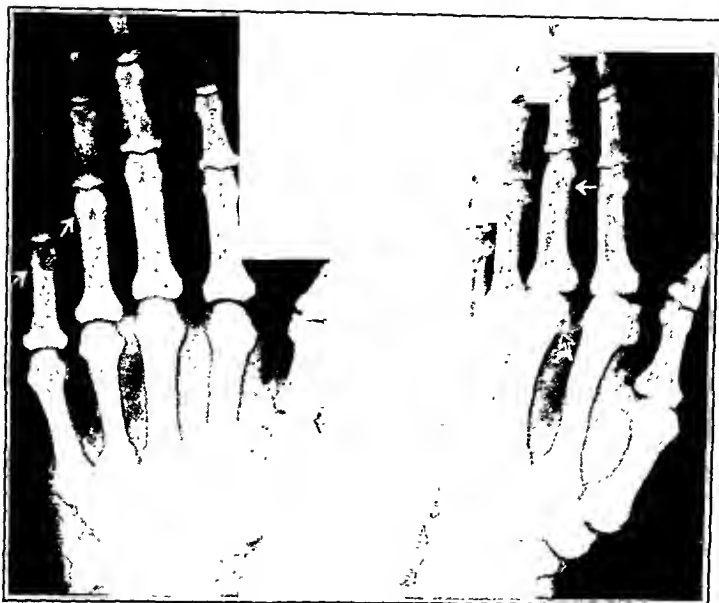


FIG. 3.—Left hand. All the phalanges and the metacarpals show marked osteoporosis. The head of the third metacarpal shows a small bone cyst.

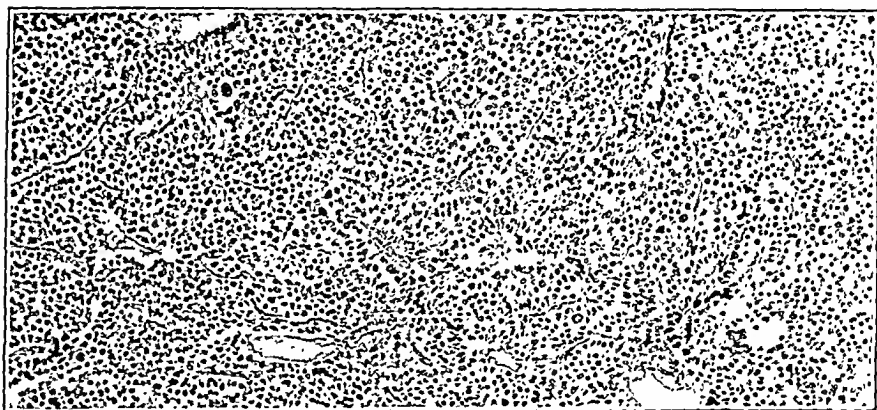


FIG. 5.—Note the hyperplasia of the parathyroid cells with predominance of the oxyphilic cells. Also note the tendency to glandular arrangement of the parathyroid cells at numerous points in the parenchyma. The spaces formed by the latter contain a colloid-like secretion which stains homogeneous pink with hematoxylin and eosin. ($\times 120$.)

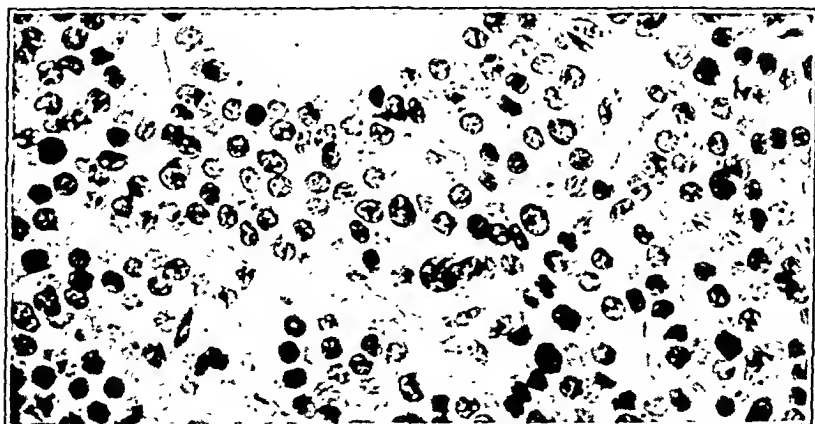


FIG. 6.—This is a higher magnification of the parathyroid tumor. Note the predominance of the oxyphilic cells and the typical glandular arrangement described above in Fig. 5. ($\times 400$.)

TABLE 1.—BLOOD NON-PROTEIN NITROGEN DETERMINATIONS.

Date.		Urea nitrogen mgm. per 100 cc.	Uric acid mgm. per 100 cc.	Creatinin mgm. per 100 cc.	Blood pressure.	
					Systolic.	Diastolic.
1934						
July 3	. . .	31.4	...	2.4	130	94
July 23	. . .	26.5	4.3	2.5	114	80
July 30	. . .	37.5	...	2.7	112	78
Sept. 12	. . .	58.8	4.7	2.7	130	90
Sept. 17	. . .	51.7	4.0	2.8	118	72
Sept. 24	. . .	49.0	...	3.2	130	90
Nov. 2	. . .		Operation			
Nov. 7	. . .	75.0	...	4.4	136	90
Nov. 10	. . .	79.8	...	4.1	134	90
Nov. 12	. . .	60.0	...	2.9	136	88
Nov. 13	. . .	66.4	...	2.7	134	84
Nov. 19	. . .	43.2	...	2.9	132	90
Nov. 24	. . .	62.1	...	2.8	120	80
Nov. 27	. . .	66.6	...	3.1	100	70
Dec. 4	. . .	57.6	...	3.4	118	90
Dec. 7	. . .	60.0	...	3.1	110	80
Dec. 13	. . .	68.1	4.2	3.3	130	90
Dec. 15	. . .	66.6	...	3.2	104	80
Dec. 27	. . .	105.0	4.7	3.8	100	80
Dec. 31	. . .	109.0	4.5	3.7	110	84
1935						
Jan. 1	. . .	120.5	4.9	3.8	80	60
Jan. 15	. . .	107.0	...	2.9	98	64
Jan. 21	. . .	89.5	4.7	2.4	90	50
Jan. 23	. . .	94.5	...	3.0	100	50
Feb. 5	. . .	50.0	4.1	2.6	100	50
Feb. 11	. . .	81.5	4.0	2.7	106	70

TABLE 2.—CALCIUM AND PHOSPHORUS DETERMINATIONS.

Date.		Calcium mgm. per 100 cc.	Phosphorus mgm. per 100 cc.	Serum Phosphatase Bodansky units.	24-hr. calcium intake gm.	24-hr. calcium urinary output mgm.
1934						
Sept. 15	. . .	19.5	6.8			
Sept. 19	. . .	19.6	6.5			
Sept. 22	. . .	17.6	6.5			
Oct. 15	. . .	16.2	6.5	6		
Oct. 16	4.06	228
Oct. 17	. . .	22.0	6.7	...	4.06	372
Oct. 18	4.43	240
Oct. 27	. . .	22.0	6.8			
Nov. 2	. . .			Operation		
Nov. 7	. . .	11.6	6.7			
Nov. 8	. . .	11.0	6.6			
Nov. 9	. . .	11.4	5.5			
Nov. 10	. . .	12.8	5.7			
Nov. 13	. . .	11.0	6.8	...	5.3	146
Nov. 14	. . .	10.4	5.4	...	5.3	98
Nov. 21	. . .	11.2	5.7	...	5.3	178
Nov. 27	. . .	10.6	5.3			
Dec. 8	. . .	10.5	9.8			
Dec. 15	. . .	14.6	8.3			
Dec. 20	. . .	9.3	7.1	4.8		
Dec. 22	. . .	11.4	8.1			
1935						
Jan. 15	. . .	11.4	7.8			
Jan. 16	. . .	12.8	8.0			
Jan. 25	. . .	12.4	7.0			
Jan. 31	. . .	11.7	7.0			
Feb. 7	. . .	14.0	7.3			

Swallowing of barium under fluoroscopy showed no filling defect of the esophagus, indicating no impingement of any tumor on the esophagus. The flat plate of the abdomen revealed no calcification, stone, or other kidney abnormality. No finely granular casts, as mentioned by Albright,⁴ were ever found.

At this time the urea nitrogen was 58.8, and the serum calcium rose to 22 mgm. on two occasions (Tables 1 and 2). A calcium balance was done. On a high calcium intake, around 4 gm. per 24 hours, the calcium output was essentially normal, varying between 228 and 372 mgm. per 24 hours. The serum phosphatase was 6 Bodansky units, normal being 2 to 4.⁸

The patient was built up by supportive therapy and transfusion, and prepared for operation, which was performed by Dr. C. L. Davidson of the Surgical Service on November 2, 1934, who reports that an adenoma of the left lower parathyroid was found, about $\frac{7}{8}$ inch in length and $\frac{1}{2}$ inch in width, with cystic degeneration. The tumor was dissected free, its blood supply was ligated, and it was excised. The right portion of the thyroid gland was explored and two parathyroids were observed. They appeared to be normal in size and consistency.



FIG. 4.—The parathyroid tumor cut in half. The darker colored upper two-thirds represents the cystlike structure, while the lighter colored lower third represents the hyperplastic parathyroid tissue.

Pathologic Report. (Dr. S. H. Polayes.) (Fig. 4.) The specimen consists of an ovoid cystic mass measuring 3 cm. in its greatest diameter. One-third of the mass is firm in consistency, and the other two-thirds of the specimen consists of a pink mass, which is cystic. Section shows the solid pole to be made up of a finely porous yellow-gray structure which tapers off into fine trabeculae, the latter traversing the cystic area to the capsule. This produces a multilocular type of cystlike structure, the wall of which is very thin, and within which is contained a brown gelatinoid fluid substance.

Microscopically (Figs. 5 and 6). The tissue consists of parathyroid, the cells of which are arranged in cords with a very fine but rich capillary network. The individual cells answer the description of parathyroid gland, both oxyphil and basophil cells being demonstrable. In areas, there is a tendency to acinar formation with an excessive colloid production. The largest accumulation of colloid is found in the cystic area mentioned in the

macroscopic description. Here the lining of the colloid collection is a thin, fibrous structure, which forms the wall of the cystic pole described above.

Diagnosis. Adenoma of parathyroid.

The microscopic slides were seen by Dr. C. F. Geschickter of the Johns Hopkins Hospital, who concurred in the diagnosis.

Following operation the patient had an uneventful convalescence, and within a few days there was a decided drop in serum calcium to 11.6. The serum calcium has remained at this level fairly constantly. The serum phosphatase was 4.8 Bodansky units. The patient has increased in weight from 83 to 98½ pounds. The deafness, which was total in the right ear and 80% in the left, has completely disappeared. Concomitant with this disappearance, the marked calcific deposits in the ear-drums have also disappeared. The epulis, which previously was large enough to reach the tooth line, has now completely disappeared, and Roentgen rays reveal an increase in osteoid tissue in the mandible, which previous Roentgen rays showed to have a punched-out appearance (Fig. 2B). Her general appearance has changed from one of anxiety and chronic illness to one of general well-being and alertness. The muscle tone has increased to normal.

Despite the marked improvement noted above, there has been no similar improvement in the kidney function. Tests have repeatedly given the same results as were obtained pre-operatively, that is, specific gravity at 1.009 and below, increased night specimen, and dye excretion between 5 and 10% after 2 hours. In addition, there has been noted an ever increasing azotemia (Tables 1 and 2). The last estimation, February 11, revealed a blood urea nitrogen of 81.5, uric acid of 4, and creatinin of 2.7.

Calcium balance determinations were made 3 weeks postoperatively. On an intake of 5.3 gm. of calcium per 24 hours, the calcium output varied between 98 and 178 mgm. per 24 hours.

This case represents one of the less common clinical types of the hyperparathyroid syndrome, which has come to be recognized as a definite clinical entity. Failure to recognize this condition results in hopeless confusion because of its close similarity to chronic nephritis, malignancy, avitaminosis, starvation and malnutrition, congenital kidney anomaly, and the various forms of generalized bony tenderness seen in scurvy in adults and bone malignancies.⁷ The outstanding features of this syndrome are: 1, Extreme wasting, despite a balanced diet; 2, azotemia without hypertension; 3, epulis, which may or may not be present; 4, high serum calcium; 5, evidence of osteoporosis, most marked in the flat bones; 6, hypotonia.

We were particularly fortunate, in this case, in finding the hyperplastic tissue in the form of one adenoma which was easily shelled out and removed. Other authors report cases of slight adenopathy in all the parathyroid glands, and even cases of hyperplasia without enlargement of all the parathyroid tissue. The latter cannot be improved by operation.⁴

In our case, there is excessive and marked parathyroid tissue hyperplasia, yet the patient has had a relatively long clinical course which has not ended fatally. The following explanation is offered for this. Cystic degeneration, as was demonstrated pathologically, has gone on hand in hand with the parathyroid hyperplasia, and

the formation of new hyperactive and hyperplastic tissue is balanced by the fact that some of this functioning tissue has undergone cystic degeneration and become functionless.

We believe in this case that the extent of the kidney damage is permanent, as shown by the fact that the urea nitrogen is still over 80 mgm. Since there is no demonstrable kidney stone by Roentgen ray, or calcification of kidney tissue or tubules, we must assume that this azotemia is due either to calcification of the glomeruli not demonstrable by Roentgen ray, or to fibrosis secondary to the chronic irritation produced by such calcification, resulting in diminished kidney function.

It will be noticed that the serum phosphorus has persistently remained high, despite the fact that the typical hyperparathyroid syndrome presents a high serum calcium but low serum phosphorus.⁵ We believe that this high phosphorus is merely another manifestation of impaired kidney function, being part of the marked kidney retention which is shown so definitely by the azotemia present.

Similarly, it is well known that in hyperparathyroidism the urinary calcium is definitely increased, while the fecal calcium remains unchanged. If there is impaired kidney function, however, the urinary calcium remains unchanged, while the fecal calcium may rise. This is described by Churchill and Cope.⁶ Thus, in our case, we attribute the normal calcium output both pre-operatively and postoperatively to inability on the part of the kidneys to excrete the calcium, although there was a decrease in the calcium output postoperatively. Unfortunately, facilities for fecal calcium estimation were not available.

Summary. A case of hyperparathyroidism is presented showing azotemia unassociated with hypertension, slight flat bone changes, epulis, and chronic wasting, successfully operated on with removal of a large parathyroid adenoma. The difficulties in diagnosis are presented and discussed. The six diagnostic features of the syndrome are listed in the hope that this condition will be brought to the attention of clinicians, so that future cases will be recognized and brought to operation.

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PELLAGRA.

AN ANALYSIS OF CASES ADMITTED TO THE PENNSYLVANIA HOSPITAL SINCE 1922.

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PELLAGRA, a word derived from a combination of Latin and Greek—meaning “rough or smarting skin”—has been recognized as a disease entity for 200 years. Caspar Casal, a Spanish physician, who first described the disease under the name of “*Mal de la Rosa*,” believed it to be due to dietary and atmospheric conditions. Since 1735 numerous theories have been advanced as to its etiology and the names under which it has been described are legion. Wheeler says, “No other disease has been known by so many aliases.” And Roberts feels that “next to lues, Pellagra is the most bizarre of diseases.” Its incidence is now known to be very widespread and yet there is little accurate information concerning it. Turner says that “Pellagra is almost unique among major diseases” in this respect.

Of the numerous theories advanced as to the etiology of pellagra from time to time, only two have survived: the infectious and the dietary. Each has its advocates but the evidence points strongly toward the latter as being in some way vitally involved. In 1912, Funk placed pellagra on the list of what he called the “deficiency diseases.” These diseases he found could be prevented or cured by the addition to the diet of certain essential food substances which he called “vitamins.” McCollum and Kennedy, in 1916, named a “growth promoting and appetite stimulating” factor, “Vitamin B.”

Much experimental work has been done on vitamin B, dogs and rats, as well as humans, having chiefly been used. Goldberger and his associates in the United States Public Health Service who did much to clarify the situation, isolated the pellagra preventive factor

(designated the "P. P. factor"). Their belief that it was related to the water-soluble vitamin B has been confirmed in the present recognition of the antineuritic or antiberiberi portion; as vitamin B (B_1 , English terminology) and the antipellagric vitamin G (B_2).

Undoubtedly pellagra was present in many localities in the United States prior to its general recognition (Wheeler). In 1864, sporadic cases were reported in New York and Massachusetts. However, the situation in this country was not appreciated until its recognition in Alabama in 1907-1908. Pellagra is especially prevalent in the Southern States, particularly in the "cotton belt" and the mill districts, where it is endemic, and at times epidemic. In these localities, the economic condition of the people is particularly poor. The evil of the "one crop system" (cotton) is reflected in the diet which consists almost wholly of a few non-perishable, comparatively cheap, staple foods of low vitamin content. Endemic pellagra makes up about 98% of all cases and is a disease of poverty.

Sporadic cases of pellagra seen elsewhere in the country are the ones which especially interest us. They make up only about 2% of the total number of cases. Wheeler states that "sporadic pellagra is due to dietary idiosyncrasies and eccentricities, food fads, obsessions, alcoholism, diseases of the gastro-intestinal tract, etc."

Pellagra does not develop until the diet has been restricted for several months—usually 3 to 6. More than 90% of the endemic cases have their onset from April to July and show spontaneous improvement in the autumn and early winter. The disease tends to recur. Most writers feel that it is not contagious or hereditary. Cases have been reported in nursing infants, but it is most commonly seen in children from 2 to 15 years in a mild form. It is more common in women than men. Underhill says, "grief, monotony, disease, constipation, domestic worries, and preparation of food are agents depriving women more than men of their appetites."

The symptoms and signs are many and varied. Bass reminds us that "Pellagra is a systemic disease." Few students forget the chief signs of the "4 D's" "Diarrhea, dermatitis, delirium and death"—an expressive and telling phrase. It is insidious in its onset, as a rule, but cases are seen of a fulminating nature.

To the early symptoms of increasing weakness and lassitude, anorexia, indigestion, sore and ulcerated mouth, diarrhea is usually added. A reduced or absent free hydrochloric acid in the gastric contents is common.

The typical dermatitis usually makes the diagnosis easy. But there are cases of pellagra without dermatitis: the "Pellagra sine Pellagra." Any portion of the skin may be affected: "any form of trauma or irritation may determine the site of the lesions; *e. g.*, radiant energy, chemical stimulus, or physical irritation" (Stannus). The lesions are usually symmetrical and well demarcated. The commonest sites are the exposed surfaces such as the dorsal aspect

of the hands and about the neck (the "necktie of Casal"). The skin becomes red and erythematous, not unlike marked sunburn. Soon pigmentation sets in with thickening, cracking, and fissuring. Secondary infection, blébs and bullæ may be seen, but the "dry type" of dermatitis is much the more common. After desquamation, the skin is pink and shiny in appearance.

The nervous manifestations of pellagra (ranging from paresthesias to marked psychoses), usually occur late in the disease.

The sporadic pellagra seen in this locality is more common than it was one or two decades ago, probably due to prohibition and the economic depression. The rôle of chronic alcoholism and its possible relation to pellagra has been much discussed. Prolonged use of distilled liquors may affect the individual in one of three ways: (1) it may destroy the pellagra-preventive factor; (2) it may interfere with the digestion and assimilation of a proper diet; (3) the appetite may be so reduced that a proper diet is not taken and the individual may exist almost wholly on liquor, usually of inferior grade. Spies and his coworkers believe that cases of pellagra found in the North are usually associated with severe alcoholism. They found that in alcoholic pellagrins the disease was usually curable when large amounts of autoclaved yeast and a full, high caloric diet was taken together with, and in spite of, a daily ingestion of from 600 to 900 cc. of whiskey daily.

On the other hand, in an earlier paper, Spies reports some interesting observations made in a series of 6 typical cases of pellagra. These cases all gave a history of low food intake and 4 of them were chronic alcoholics. They were hospitalized and placed on a carefully controlled diet which was lower in mineral and vitamins C, D, and G content than Goldberger's so-called "pellagra-producing diet." In 5 of the 6 cases, the skin lesions cleared up rapidly. The author writes that "possibly a secondary factor is involved in the production of the disease."

Lesions of the gastro-intestinal tract, interfering with proper nutrition, account for some of the sporadic cases of "pellagra." Ellis feels that any sporadic case which does not respond to proper dietary treatment should be carefully examined from the gastro-intestinal point of view for a pathologic condition which might account for the disease.

The relation of pellagra to Addisonian anemia has been raised. Spies and Payne have proven experimentally that the diseases are distinct. They took the achylic gastric juice from 2 cases of acute pellagra, on a vitamin G-free diet, and incubated it with beef. When this mixture was given to 2 patients suffering from Addisonian anemia, a characteristic reticulocyte response was noted showing the presence of Castle's "intrinsic factor." Absence of characteristic changes in the red blood corpuscles and hemoglobin of pellagrins

with an acidity adds further weight to the assumption that the 2 diseases are of different natures.

For efficient treatment, an early diagnosis is most important. After structural changes have set in, the outlook is much less favorable. A careful and accurate history is especially necessary where cases are seen only sporadically, otherwise the possibility of pellagra will be overlooked. The question of diet must be gone into thoroughly, for the crux of the situation is what the patient actually eats and not what his table or circumstances offer.

Pellagra patients at this hospital are put on a full, high-caloric, high-protein diet, rich in vitamins. To this is added fresh yeast obtained from a brewery in doses of 4 to 6 drams 4 times a day. If diarrhea accompanied by low or absent hydrochloric acid is present, dilute hydrochloric acid in doses of $\frac{1}{2}$ to 1 dram, well diluted in water and taken through a glass tube, is given with the meals. Patients giving a history of chronic alcoholism are allowed alcoholics in gradually reduced doses until the alcohol can safely be eliminated. The skin lesions are treated with a bland ointment unless secondarily infected. The latter, if present, can be cleared with dilute permanganate soaks or wet dressings. If anemia is present and severe, large doses of iron and ammonium citrate (25%) are often given. Liver extract, intramuscularly, also in large doses has been used with good results.

Underhill's experiments with dogs indicate that the addition of vitamin G to the diet is a much better prophylactic than a curative measure. Once the condition of pellagra is well established or advanced, *i. e.*, when structural changes have set in, he feels that hope for a cure is much more remote.

In treating sporadic cases, Roberts feels that encouragement and even psychotherapy are often very important in order to obtain a good result. He adds that the patient must be convinced that his symptoms, such as indigestion, weakness, diarrhea, etc., are caused by the lack of an adequate diet. All too often a patient feels that his troubles are due to the taking of certain foods which are one by one abandoned until the diet is almost completely curtailed, and, instead of improving, the condition becomes steadily aggravated.

The following small series of cases have been observed in the wards of the Pennsylvania Hospital from 1922-1935. In each case, the diagnosis of pellagra was made, and all but 3 have been admitted during the past 2 years.

Case Abstracts. CASE 1.—M. R. (No. 6485), a colored female, aged 32, was admitted February 7, 1922. A native of Florida, she came to Philadelphia 2 years prior to admission. She complained of loss of appetite and weakness. Her weakness dated back to an attack of influenza in 1918 and since that time she "had never been herself." She became increasingly weak and nervous and had been bedridden since August, 1921. The appetite became steadily worse and considerable weight was lost. She gave no

history of alcoholism. Her diet, due to economic circumstances, was limited, and considerable corn bread was eaten, but not exclusively.

Examination revealed a markedly toxic and emaciated negress. She was irrational and suffered from delusions. There was marked injection of the mucous membrane of the mouth and pharynx with areas of ulceration. There was a symmetrical, bilateral pigmentation of the malar bones and dorsal surfaces of the hands and wrists.

Laboratory examinations were negative except for a strongly positive blood Wassermann reaction.

A diagnosis of pellagra was made but the patient made little progress and signed her release from the hospital February 23, 1922, unimproved.

Since this patient had only been in Philadelphia for 2 years prior to admission and had been ill during her entire stay, she probably was suffering from pellagra before she came North.

CASE 2.—B. B. (No. 1333), a white male, aged 37, was referred here May 1, 1923 from Snow Hill, N. C., with the diagnosis of pellagra.

The patient complained of "bowel trouble," which he said he had had since he was 10. This and diarrhea were especially severe early in the spring and summer after which they would tend to improve (very suggestive history). The year prior to admission, his condition became much worse and there was no seasonal change. He had been passing 10 to 12 loose, watery stools daily; these nearly always showed a little red blood. The appetite on admission was good, and his diet included eggs, cheese, fish, butter, white bread, soda crackers, biscuits, and some corn bread. He had eaten no vegetables and little meat the year prior to admission because they "upset his digestion." His best weight was 160 in 1911, and on admission he weighed only 100. In 1911, he had some "eczema" on his chest, forehead, and cheeks, which was red and itched some. This eruption was not constantly present, but would come and go. He also contracted the "ground itch" about 1911. About 4 years prior to admission, dermatitis appeared on the backs of his hands, which "comes on especially in spring and when the sunshine is hot." The skin involvement disappeared during the late fall and winter only to return the following spring.

The patient was a farmer. He stated his mother was in an asylum. He also stated that he drank "a little whiskey."

Physical examination revealed a poorly nourished, emaciated white male, who was drowsy. The tongue was smooth and very red. The abdomen was tender throughout. There were numerous, small, discrete, pigmented areas of dermatitis on the exposed dorsal surface of the hands extending to the wrists.

Laboratory examination revealed a marked secondary anemia. Stool specimens were positive for occult blood. Hookworm ova and the *Strongyloides intestinalis* embryo were also present. The urinalysis showed nothing abnormal. The blood Wassermann reaction was negative.

Efforts to control the diarrhea and rid the patient of his intestinal parasites were not successful and he failed steadily. He died, after being irrational for 2 days, July 19, 1923.

CASE 3.—V. B. (No. 7748), a colored female, aged 29, a native of Florida, who had lived an unknown period in the North, was admitted to the wards on 3 occasions from October 25, 1928, to February 25, 1933. Between admissions she was followed in the Outpatient Department.

Her chief complaint was constipation, first noticed in 1924. She got along fairly well until 1927 when she had to resort to purgatives in order to obtain soft, watery stools. On her first admission (1928), her bowels would only move after purgation and straining, accompanied by a sense of constriction in the anal region. Her appetite was good but she was "afraid to eat on account of difficulty in moving the bowels."

Physical examination at first was negative, except for a stricture of the rectum about 1½ inches proximal to the sphincter. This was dilated under general anesthesia and the patient was shortly discharged, greatly relieved.

She was readmitted January 11, 1933, with the same complaints and diagnosis. The interval history stated she had been well following her discharge in 1928 until 1930 when the old symptoms returned. She suffered increasing weakness, loss of weight, chills and fever and progressive constipation, with all stools containing blood, mucus and pus. She had lost considerable weight, and her blood count showed 30% hemoglobin and 2,600,000 red blood cells. The skin was dry and dehydrated but as yet showed no lesions. Dilatation of the stricture was again resorted to. The Frei test for lymphogranuloma inguinale was suspiciously positive. She was discharged to the Outpatient Department, improved, January 28, 1933.

Her final admission came only one month later, February 25, 1933. She had become much worse and her emaciation and dehydration were marked.

She was transferred to the Medical Ward March 17, 1933, when a symmetrical, dry, pigmented dermatitis, extending up to the wrist, was noted on the dorsal surface of the hands. Later, similar skin changes were noted at the elbows. Her course was progressively worse and 1 week prior to death, the patient became demented.

Laboratory Data. Blood Wassermann test negative. Marked secondary anemia. Volume index, 0.77. Fractional gastric analysis showed a normal amount of free hydrochloric acid. The urine showed 1+ albumin and an occasional hyalin cast.

At autopsy (Dr. J. S. Taylor, 3 hours after death), the following conditions were found: (1) pellagra; (2) extensive ulcerative colitis involving the descending colon, sigmoid and rectum with fibrosis and narrowing of the lumen for the distal 7 to 8 cm. with stricture formation; (3) acute purulent peritonitis.

This case is the most unusual and interesting of the series. Pellagra developed secondarily to a lesion of the gastro-intestinal tract, which markedly affected nutrition and digestion. The lesion was a rectal stricture caused by lymphogranuloma inguinale.

CASE 4.—M. M. (No. 31059), a white woman, aged 54, native of Philadelphia, was admitted July 16, 1934, complaining of fatigue and nervousness, with pigmentation of the backs of the hands and anterior portion of the neck and chest. Her appetite had been very poor for 2 or 3 months prior to admission and she had eaten a lot of candy. Three days prior to admission, after washing clothes, she noticed that the backs of her hands were pigmented and somewhat painful. She attributed this to the use of laundry soap (the same brand which she always used) and the effect of sunlight. The skin of the neck and chest became involved at the same time. The involved area "burned" her.

Her bowels moved 2 or 3 times daily. There was no diarrhea and only occasional indigestion. Her diet, prior to admission, had been reduced, due to poverty and for sometime she had lived chiefly on bread, butter, tea and coffee. She gave no history of alcoholism.

Physical examination revealed a faint, reddish-brown pigmentation over the malar bones. The tongue and lips were very red. There was an area about the size of the palm of the hand on the anterior chest below the clavicles and the suprasternal notch which was reddened, desquamated, and indurated. Over the entire dorsum of the hands extending just above the wrists was a brownish-red, desquamating pigmentation of the skin. The ankles were also pigmented.

Laboratory Findings. Urine, normal. Blood Wassermann test negative. There was no anemia. Free hydrochloric acid was present in the gastric contents. Serum protein was 5.6%.

Under treatment, the patient improved rapidly and was discharged October 6, 1934.

CASE 5.—L. S. (No. 33137), a colored female, aged 36, native of California who had resided in Philadelphia for an unknown period, was admitted to the Ward, January 15, 1934, complaining of weakness, diarrhea, dermatitis and an abdominal mass.

Her diet, for a year prior to admission had consisted almost entirely of bread, soups, and cereals. Her appetite began to fail in November, 1933, and she felt increasingly tired and listless. This was followed by soreness of the mouth and a burning sensation of the hands, plus the appearance of dermatitis on the dorsal surface. One week prior to admission, diarrhea set in. There is no history of alcoholism.

Physical examination revealed pigmented areas, almost black, with cracking and fissuring on the backs of the hands and wrists. Similar areas were present on the dorsal surface of the feet and about the genitalia. The tongue was markedly reddened with whitish plaques on the dorsum and about the frenum. The uterus contained several fibroid tumors.

Laboratory Findings. There was a moderate secondary anemia. Urine, normal. Blood Wassermann test negative. Free hydrochloric acid was present, but reduced, in the gastric contents. The stools were positive for blood.

In spite of the usual treatment, the patient became steadily worse, and died January 30, 1934.

AUTOPSY (Dr. A. D. Wallis, 3 days after death). A few of the findings are presented: "A scaly dermatitis was noted at the angles of the mouth and on the dorsum of the hands including the fingers and a short distance beyond the thenar surfaces of the wrists. This was deep brown, almost black, with moderate scaling, and areas of bleeding ulcers. Microscopically, the papillæ projected downward, deeper than usual, and pigment production of the lower layers was definitely increased. Round-cell infiltration was scattered throughout the upper layers of the corium and as deep in places as the subcutaneous tissues. Nothing except a moderate amount of cortical atrophy was noted in the brain. Death was probably due to pellagra.

Pathologic Diagnosis. (1) Pellagra; (2) multiple leiomyomata uteri; (3) old chronic bilateral salpingitis.

CASE 6.—J. H. (No. 34662), a white male, aged 54, native of Philadelphia, was admitted June 1, 1934, complaining of burning of the backs of the hands of 12 days' duration. Six years prior to admission, following a prolonged diet consisting chiefly of "stews" and no vegetables, the patient developed a dermatitis on the dorsal aspect of the hands and suffered from diarrhea. He was told he had pellagra and was followed in the Outpatient Department of the Hospital. In 6 months, he had apparently completely recovered with treatment and an improved diet. He had been well until 12 days prior to admission when the diarrhea and dermatitis reappeared. The patient had been unemployed for 2 years and his diet for 6 months before admission consisted chiefly of pork and potatoes, plus a heavy and consistent consumption of alcoholics of a poor grade.

Physical Examination. The patient's mental state was active. There were widespread ulcerated patches of pigmented skin on the dorsal surfaces of the hands up to the wrists.

Laboratory Findings. Urine showed 1+ albumin. There was no anemia. Fractional gastric analyses showed achlorhydria. The blood Wassermann reaction was negative.

The patient showed rapid improvement upon withdrawal of alcohol and bettering the diet and nutrition with the usual methods mentioned. He was discharged June 18, 1934.

CASE 7.—L. E. (No. 34839), a colored female, aged 31, native of North Carolina, whose stay in Philadelphia is not known, was admitted June 18, 1934, complaining of pain in the chest, fever, sore mouth, and loss of appetite with dermatitis of the hands. The history was indefinite as to the duration of the loss of appetite and the presence of dermatitis, but for several months the patient had consumed large amounts of alcoholics and eaten very little.

Physical Examination. The tongue and pharynx were very red. There was desquamation and hyperpigmentation on the backs of the hands and wrists. No changes were noted over the neck, feet, or genitalia.

Laboratory Findings. Urine, normal. Blood Wassermann test negative. There was a slight secondary anemia. Gastric analysis showed no free hydrochloric acid.

The patient made an uneventful recovery upon the withdrawal of alcohol and the substitution of proper diet and treatment.

CASE 8.—D. D. (No. 35068), a colored male, aged 77, native of Philadelphia, was admitted July 8, 1934, complaining of vomiting, diarrhea, and itching of the skin. He was very poor, and had no one to care for him. For several months prior to admission, he had lived on cereals and rice chiefly. He had suffered from pruritus for 3 months before entering the hospital, but the vomiting and diarrhea were only of a few days' duration. There was no history of alcoholism.

Physical Examination showed areas of rough, desquamating hyperpigmentation on the dorsal surface of the hands and wrists, also over both ankles. It is of interest that the patient attributed his dermatitis to sunburn.

Laboratory Findings. Urinalysis showed 1+ albumin with an occasional cast and red blood cell. There was a slight secondary anemia. The blood Wassermann test was negative. Fractional gastric analysis showed a hypochlorhydria.

CASE 9.—S. P. (No. 35456), a white male, aged 48, native of Philadelphia, was admitted August 17, 1934, complaining of weakness, loss of appetite, and failing vision. He was in good health until 4 months prior to admission when he began to drink heavily and steadily. He consumed from 1 to 3 pints of cheap whiskey daily and began to suffer from increasing weakness, loss of appetite, and failing vision. One month before admission he noted redness and roughness of the backs of his hands and he passed 6 to 7 watery stools daily.

There was a loss of 40 pounds in 4 months, and the patient stated he had eaten more during his first 3 meals in the hospital than he had during that entire period. The patient was a mattress maker, unemployed for 9 months. He had only occasionally partaken of alcoholics previously.

Physical Examination showed rather marked emaciation. On the dorsal surface of each hand, extending up to the wrist, was a rough, scaly, symmetrical, pigmented dermatitis.

Laboratory Findings. Urine, normal. There was a mild secondary anemia. The blood Wassermann test was negative. Gastric analysis showed an achlorhydria.

Under treatment there was a progressive clearing up of the diarrhea and dermatitis. It was thought that the patient had an alcoholic neuritis of the legs as he complained of tenderness along the nerve trunks. After considerable rest, baking and massage were instigated; and the patient was discharged, much improved, to a convalescent home, October 18, 1934.

CASE 10.—W. J. (No. 36722), a colored male, aged 28, native of North Carolina, had been in Philadelphia 7 years before admission. He entered the ward, December 30, 1934, complaining of pain and tenderness in the soles of his feet, diarrhea, and abdominal distress. He had been perfectly well

until 3 months prior to admission when he began to suffer from weakness, loss of appetite, and paresthesias of his feet. His bowels moved 3 times a day and he felt dull and apathetic. Three weeks before admission, the patient began to suffer from diarrhea and abdominal distress. There were 15 stools daily; and at times, tenesmus was present. At this time, the patient noticed a dry, scaling, atrophic dermatitis on the backs of his hands and wrists and also about the ankles.

He gave a history of having consumed a pint of cheap whiskey daily for a period of 18 months to 2 years with a corresponding reduction of diet. His diet consisted chiefly of a small amount of canned meat and vegetables with occasionally fresh fruit.

Physical Examination showed a mentally dull, young, colored male, lying flat in bed. He was dehydrated and had a slight odor of acetone on the breath. There was oral sepsis, and the pharynx was diffusely injected. Glossitis was present with atrophy of the papillæ and tremor. There was a dry, scaling, pigmented dermatitis on the dorsal surface of the hands, extending up to and including the wrists. The skin was desquamating in thin sheets. There was hyperpigmentation over the malleoli and dorsal aspect of the feet with desquamation. The anterior surface of the neck and chest showed hyperpigmentation, but the distribution was not that of the typical "necktie of Casal."

Laboratory Tests. Urine, normal. Blood Wassermann test strongly positive. Stools, moderately positive for blood. No anemia was present, but 16,800 white blood cells were found.

The patient is still in the ward, but has made a gradual progressive recovery, and is soon to be discharged.

Discussion. Although pellagra has been known for 200 years, it has not been until the past three decades that its presence and seriousness in the United States has been given much attention. The disease is a serious one. Wheeler reports that in 1930, there were 7146 deaths from pellagra in this country, and that for each death 35 persons were disabled.

Pellagra is endemic in the South and its presence in that locality is far more common than in the North. In spite of an increase in the incidence of the disease in recent years, the author believes that many cases in the North are overlooked. Like syphilis, pellagra is a bizarre disease. Medical schools teach us to be "syphilis-conscious"—we should also be "pellagra-conscious." The classical case is recognized by any physician, but pellagra often does not make a classical appearance. We are too prone to think of the condition as only affecting the dermal, gastro-intestinal, and nervous systems—forgetting that the disease is systemic.

For years the etiology of pellagra has been argued and the point has never been definitely settled in spite of a great deal of experimental work. Dietary deficiency *versus* infection is still a moot question.

Pellagra is primarily a disease of poverty and ignorance. However, members of the more well-to-do classes of society are not immune and frequently, have some very strange ideas about the question of diet. A careful history in obscure cases is essential.

The important thing to learn is what the patient under observation actually eats and not what his table or circumstances offer.

Pellagra is an insidious disease in most instances. It tends to be seasonal, to recur, and to show remissions. The physician should be alert for its appearance, or cases are sure to be overlooked.

All of our cases seen at the Pennsylvania Hospital since 1922 have been ward admissions.

Case 1 is a case of Southern endemic pellagra, who had been ill during her 2 years in Philadelphia. Unfortunately after 16 days' hospitalization, she left unimproved.

Case 2, also was a Southern endemic case. His pellagra was complicated by infestation with hookworm and strongyloides intestinalis. Nothing could be done for this patient whose condition, when seen, was advanced; and he succumbed.

Case 3, to me, is the most interesting one of the series. The patient suffered for 10 years from a rectal stricture which had to be dilated, under general anesthesia, on 2 occasions. The stricture was secondary to lymphogranuloma inguinale. Not until shortly before death did symptoms of pellagra appear. The patient had gradually reduced her diet and resorted to more purgation in order to keep her intestinal canal open.

Cases 4, 5, and 8 developed pellagra secondarily to diets wholly inadequate as to vitamin content, taken over a long period of time because of poverty. Cases 6, 7, 9 and 10 developed the disease after existing over considerable periods on liquor of poor grade with a simultaneous marked reduction of proper food.

Summary. Ten cases of pellagra seen on the wards of the Pennsylvania Hospital since 1922 have been reviewed and discussed. All but 2 were admitted during the past 2 years. The author feels that there has been a real, rather than an apparent, increase of pellagra in the North during recent years. Prohibition, with its attending increase in inferior grades of alcohol, and the economic depression are believed to be causative factors.

Of the 10 cases reviewed, 2 had developed pellagra in the South where the disease is endemic. Of the remaining 8 sporadic cases, all seen during the past 2 years, 4 were native Philadelphians, 1 had lived in this city for 7 years, and the duration of residence of 3 is unknown.

Prolonged restriction of food intake, due to poverty, was the etiologic factor in 5 of the cases. The disease developed following chronic alcoholism in 4 cases, and secondarily to a gastro-intestinal lesion in 1 case. Autopsies on 2 of the 3 fatal cases are presented.

Pellagra, as it often does not present the characteristic picture, may require great diagnostic acumen. A carefully detailed history, especially as to amount and kind of food actually eaten, is essential. The condition has become more common in the North in recent years but it is felt that obscure cases are frequently overlooked.

It is hoped that physicians will become more pellagra-conscious and attack the menace early before the disabling structural changes have set in.

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THE PSYCHOLOGIC BACKGROUND OF COLITIS.*

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ONE of the ideas I do want to put forward is that ulcerative colitis may be the end result or organic consequence of functional disorder of the colon. Let me give you an analogy: The late Dr. Crookshank¹ used to classify angina into three types: (1) The false or hysterical: 95% functional and 5% organ inferiority. (2) The more severe: 33% poisoning, 33% functional, 33% over-

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strain of cardiac muscle. (3) Angina gravior: 5% functional, 95% gross disease. I believe that colitis by analogy can be classified in a similar fashion into functional, intermediate and ulcerative. (The *Lancet* speaks of colitis gravis.²)

Much research has been carried out into causes of ulcerative colitis and much bacteriologic ingenuity has been exercised in order to incriminate this or that particular coccus without very convincing results.³ Surely what has been overlooked is that with the few exceptions of fulminating infection,^{4,5} the ulcerative stage is a terminal condition and the infection would not have taken place except in a colon already disorganized by repeated dysfunction.

We must realize that to speak of curing a patient of ulcerative colitis is to make a claim as unreasonably impossible as to speak of curing coronary thrombosis or malignant hypertension. Jones⁶ only claims 10% of cures. The truth is that such patients are incurable. Gross organic changes have taken place in the mucosa of the bowel, in the myocardium, in the elastic tissue of the arteries and palliation is the most that one can expect. But prevention of these terminal states can be attained if the functional disorder is recognized in good time and as partly an expression of an emotional state.

What I hope to do is to illustrate the stages by which the patient and his or her colon graduates in despair and degeneration from functional disability to gross organic lesions. We must bear constantly in mind that the patient cannot be separated from her colon, or the emotional state from the somatic symptom.

It will be useful to introduce another analogy at this stage. When faced with a case of sexual impotence or ejaculatio precox, we do not rush at the patient with a urethroscope to examine the verumontanum or inject his vesiculæ seminales with lipiodol.⁷ There is, of course, a type of mind which holds that seeing is believing and such procedures are still carried out in certain quarters. But most of us here I think would begin by attempting to assess the patient's attitude to sexual function as a more useful approach to the problem. In like manner I would suggest that in dealing with a patient reporting symptoms of dysfunction of the colon the case investigation is incomplete if the physician has failed to ascertain the patient's attitude to bowel function. The objective physician may smile at this invitation to the patient to give free rein to his fancies, but I do maintain that useful information is lost by not taking advantage of this subjective approach. For such an attitude does exist, of course, and one has only to read the advertisements in the daily press or even the reputable scientific journals to realize that some of the manufacturers of laxatives and aperients deliberately cultivate this attitude of mind.

You must have noticed the general tendency in these advertisements to project on to the large bowel the ideas of impurity, of bad

habits, of sluggishness. As children our "nannies" used to tell us when we were in sulky moods that there was a little black man on our shoulders. Now the aperient mongers try to convince us that all our depressions, lassitudes, lazinesses are due to the big black tube inside us. But as we agree that regression may play a big part in determining the nature of our illnesses, it may be useful for a few minutes to analyze the way in which we are instructed to regard bowel function. I do not propose to be subtle, or Freudian, about this, or to talk about anal erotism, but rather to present to the actual sequence of events.

The first impression, I suppose, of a breast-fed baby after an action of the bowels is that he feels very uncomfortable. He calls for assistance—his cries are generally effective and bring his mother or nurse on the scene. And so we have defecation—discomfort—call for help—mother. And I think there is some evidence that, like Pawlow's dogs, who salivated at the sight of food when the bell was ringing, and later were conditioned to the bell, so, in some infants, at any rate, an association is established, making defecation a call for help or attention.

The other conditioned reflex which may be established in infancy is the emptying of the bowel which takes place when the infant is frightened. One pediatrician claims that a great deal of the diarrhea in children's wards in hospital is not infective at all, but is a fear reaction, due to frequent handling by strangers. He claims that the small infant, handled by a probationer rather than its mother, and constantly disturbed with unfamiliar rites, such as temperature-taking and physicians' examinations, is likely to empty its bowels frequently, and such diarrhea can be eliminated by a picked staff of nurses infrequently changed who handle the infants carefully and economically.

The next psychologic factor in the development of bowel function is that invoked in the training of the infant to a regular reflex. This is practically the first demand made by Society—through the mother or nurse on the infant. The child soon learns that if it delivers the goods it receives encouragement—that if it fails to respond, displeasure, even annoyance may be exhibited by its guardian. And so it finds that by its bowel function it can provoke varying emotions from its personal environment.

It has discovered a new channel for exercising power. Quite apart from question of diet, many cases of constipation in children over 6 months old exhibit this factor of purpose. The infant can realize its power of attracting attention by refusing to comply with the demands of Society. And some of the cases of incontinence of feces are the end result of this particular practice.

Case Reports. CASE 1.—A bright child, aged 3 years, was the younger sister of an epileptic boy whose mother was devoted to him and spent all her time and care on the boy, rather to the neglect of the daughter. The

daughter's response to this situation was constipation which had the desired effect of focusing the mother's anxious attention on her. The defecation stimulus was neglected to such a degree that it was only by voluntary effort that the stool was retained. But when the child's attention was diverted at play, a stool was often involuntarily passed, whereupon she would burst into tears of rage and vexation. Here the rectum, under the influence of emotion, is being trained, as Schilder¹⁶ would say, in a pathologic direction.

And this brings us to the point where moral factors are introduced. The baby is told she is a good girl when she obliges with a stool at the correct time, and not uncommonly that she is "bad" when the pot is found to be empty.

It is, to say the least, significant that the first notions of goodness and badness, or good and evil, are associated in the child's mind with the production of a stool. That this association does persist into adult life is quite evident to me. Numbers of patients come to me because of alleged constipation. Often, as Hardy⁸ points out, Roentgen ray examination reveals an accelerated passage of barium through the bowel in a patient who has been taking purgatives daily for relief.

CASE 2.—A married woman, aged 43, complained of constipation. She was brought up by a very strict mother who incidentally was not so strict with a younger sister, and was "her father's girl." (She says her father was constipated.) As a baby she had colic and screaming attacks, and was constipated when at school, at the factory, and since marriage. Her mother gave her senna and castor oil regularly. Her happiest time was at the factory, but before she was 19 she was kept at home by her parents, as her mother was pregnant with her youngest sister and the patient had all the nursing to do.

She married 10 years later, but not happily. A miscarriage followed after 3 years, and since that date no pregnancy has occurred. Last year she went back to live with her parents. She still feels her youngest sister is the favorite. She complained of many abdominal discomforts which she rationalized as due to the "constipation," but a barium meal showed that the meal was hurried out of the stomach and was in the rectum in less than 6 hours. I feel that the imagined constipation in this case was a protest against the strict mother's favoritism.

CASE 3.—Another conscientious clerk consulted me for constipation, for which he had taken purgatives for years, and prescribed for himself a diet which drove his wife almost distracted (surely a purpose there). He was outraged when I suggested to him that he leave off his aperients. He could hardly have been more shocked if I had recommended him to seek extramarital intercourse. It was quite obviously a moral question with him and his rather rigid mind had grown up to think that it was wrong to be constipated and he disapproved strongly of my advice to allow evil that good might come. Such people are like those Pharisees without understanding, who still believe the tradition of the Elders. For them the text obviously runs "out of the colon proceed evil thoughts, murders, adulteries, fornication, thefts, false witness, blasphemies," etc., and to such people I reply by telling them of the patient I had in hospital.

CASE 4.—The patient was a case of anorexia nervosa, and admittedly her food intake was small. Aperients and enemata I considered contraindicated and, as she was under observation in hospital, I allowed her to go 16 days

without a stool. During that time she had no headache or marked distention, and on the 17th day had a natural action and followed this up by establishing a rhythm of natural defecation every third day. Roentgen rays showed that she was not a case of Hirschsprung's disease.

While in some cases the trouble originates in the child demanding more attention from the parent, in others it is the parent who is responsible for determining an emotional association. Over and over again we all hear in the outpatient departments: "Do you have to give the child opening medicine?" "Oh, yes, I give him syrup of figs every Saturday." "Why? Does the child miss an action of the bowels on Friday?" "Oh, no, Sir, but I thought I ought to." Here again we have this notion of right and wrong; this time in the parents' mind. It would be wrong to let our Ernest get constipated, and so Ernest after suffering the weekly ablutions externally, also suffers internal pangs of purification on Saturday night, and thus is brought up to believe *qu'il faut souffrir pour être pur*. A weekly punishment is inexorably demanded, and he can only avoid this by diarrhea.

This fuss and bother about constipation as if it were a crime is well illustrated by the following case:

CASE 5.—Two years ago a mother brought her daughter, aged 18, to my outpatient department for the most obstinate constipation. The girl looked pale and atonic and complained of backache, which she stated was worse after stool (a protest against defecation?). A skiagram of the lumbar spine and pelvis was negative. Rectal examination was negative. The mother told me that she herself had phthisis and could do no housework, so that her daughter looked after the household, of father, invalid mother, 4 brothers and a younger sister. The mother was evidently very obsessed about the constipation, and the girl told me subsequently that the whole family were concerned over the action of her bowels, and that it was a matter of diurnal inquiry by each and every member of the household. When she came to see me, she had already lost her appendix at 15 and her coccyx at 16 in the quest of a cure. From the bullying manner of her mother, who now demanded a colectomy, I strongly suspect the wretched family physician had arranged these previous operations in self-defense. The girl, of course, had not improved as a result of these mutilations. Her mother told me that her daughter was not inclined to go outdoors, had no interest in boys and her sole amusement was in the activities of the local parish church. Her mother said she was good tempered, and did not grumble. I thought her sullen. Roentgen rays showed normal progress until the colon was reached; then some delay; a partial evacuation at 72 hours and great distention of the rectum with final evacuation after 110 hours. The descending colon showed excessive haustration. I think this girl had certainly acquiesced with the domineering diagnosis, just as she had accepted without enthusiasm the rôle of household drudge. Her interesting complaint which defied all doctors served as an introduction to various hospitals, where she lay uncomplaining for a few weeks each year while her malady was investigated.

I learned recently that this struggle had a further sequel. The mother, insisting that this constipation must be cured, persuaded a fresh surgeon to do a sympathectomy. The daughter, passively resisting, "I won't be cured," survived the sympathectomy without any alteration to the con-

stipation much to the surgeon's chagrin, and the mother, who still refused to acknowledge defeat, roundly abused the surgeon for his unsatisfactory intervention.

It is not difficult to foresee the organic end result in this case. I believe this patient with her enormous dilated rectum, which practically fills the pelvis, will ultimately develop into one of those cases of dolicho colon, and each loop will make the mass reflex more difficult. The bowel will become more overloaded. Fresh flexures will develop until the picture of redundant colon is fully developed.

This curious childish submission to the maternal diagnosis was again illustrated in another case of "colitis." The last patient had not become adult enough to be interested, or at any rate to admit her interest, in boys.

CASE 6.—This patient, a woman aged 33, had got as far as getting engaged. She had, however engaged herself to a fiancé of whom her widowed mother and army brother most strongly disapproved. In fact, the patient must have had some doubts herself, for every time he came to visit her, even when she was away from the family at a convalescent home, she felt "sick" and she passed loose motions.

She had been sent into my ward with a diagnosis of tuberculous peritonitis, which had been hailed with satisfaction by her brother, who, on learning the diagnosis, told the fiancé that his sister would be an invalid for the rest of her life, and the engagement must be broken off. Her early history was that she had always got on better with her father than her mother. Her father died of a duodenal ulcer when she was 14. She said that hit her very hard. Her mother was very affectionate and demonstrative, but there was always friction at any manifestation of her daughter's independence; she would not admit that either daughter or son had grown up.

When she was 20 her mother's nerves became very bad. The patient woke up one night with abdominal pain and vomiting. Appendicitis was diagnosed. The mother and family doctor were nervous and wanted to be on the safe side, so she was sent away for a seaside holiday.

She improved until the day after her return to home, when she had another attack of pain. The appendix was removed, but the incision took a long time to heal up; there was no sepsis. The skin flaps failed to unite. For the next 2 years she was treated as an invalid, and it was only at the age of 24 that she began a belated training as a teacher. She met her fiancé, a worthy but impecunious young man, when she was 32, and became engaged almost at once, but put off announcing the dread fact to her family for 6 months. Then the storm broke. The brother, an officer in a famous regiment, was horrified; he claimed he should have known about it before, and in his best parade ground manner told his would-be brother-in-law that he was a cad. Her mother insisted that if she persisted in marrying this man the family would have to keep him.

Two months of these family rows had their effect, and one morning my patient fainted in her bath. She was put to bed, and when she got up again she noticed a dragging pain at the appendicectomy scar. Each day for a week she rose from her bed and promptly subsided in a faint. The family doctor was called in. Roentgen rays were advised. Some calcified glands were found in the abdomen. A 4-hourly temperature chart showed some fever, and there was the diagnosis of tuberculous peritonitis. But I found that mental excitement had always sent her temperature up and brought on loose actions of the bowels ever since she was a little girl. When she was sent to my wards she had accepted the rôle of the incurable

invalid, and was quite upset when I questioned the diagnosis. For that involved taking up the struggle again, coping with disapproving mother and brother and marrying her fiancé. But I was able to demonstrate her flight into illness to her satisfaction, and I was pleased, a year later, to receive a grateful letter of thanks, stating that she was happily married.

I have another example of a widow—only daughter situation.

CASE 7.—This was a girl, aged 20. Her father had died when she was 5. She was the middle child, the other 2 children being brothers. She had always suffered from stomachache when frightened. Apart from her bereavement, she had experienced an uneventful childhood. She took a little time to settle down at school under a strict headmistress, and became a typist at 16. She dropped athletics on leaving school. She would have liked to play tennis, but could not afford it. She found officework uncongenial and grumbled at having to earn her living. On her holidays she stayed at home reading a book. She had very few friends, girls or boys. When she was 19 she had some hemorrhage from the rectum, and was treated for hemorrhoids. Later she suffered abdominal pain and began to pass mucus. After 2 months in bed, she was admitted to one of the teaching hospitals and sigmoidoscoped. Nothing was found except a mucous membrane studded with small bleeding points. She recovered after a seaside holiday, and went back to work for 9 months, and then relapsed.

After another 2 months of passing blood and mucus, she was admitted to my wards. I found her very controlled and unemotional. She was not in the least worried about her illness, and stoically put up with the abdominal pain, behaving like a well-brought-up child. I could not elicit any admission of worry or distress. She owned she was bored with her job and the family poverty. A skiagram showed complete loss of haustration of the colon. Not a single sacculum was to be seen from end to end. After six weeks in hospital she improved very considerably, and some days passed without any discharge from the rectum.

Rather significantly, on learning that she was to be discharged, the stools rather rapidly increased again.

This girl had been brought up in a fatherless household, by a woman of considerable personality. Although very attractive in a rather babyish way, she was significantly lacking in the natural interests of youth. She had made no effort to cope with sex, or society, and had retreated from the problem of earning a living. The increase of diarrhea before leaving seemed to hint at a reluctance to return to the rather overpowering influence of her strong-minded mother.

CASE 8.—My next patient had gone rather farther than the last case, for not only had she found a boy friend, but she had permitted matters to progress so far that she had become a mother. This was unfortunate, as she had dispensed with the preliminary legal formalities. However, she was carrying on the family tradition, as she had been brought up in an institution for foundlings, and had never known her mother. Not very intelligent, she had not recognized her condition for some months, but soon after discovering what was the matter she began to pass blood and mucus per rectum. No characteristic organisms were recovered and she was admitted to hospital; the "colitis" cleared up after parturition. I was allowed to investigate her case history by the courtesy of Dr. Phillips, of the Southmead Municipal Hospital. She was suspicious and I was unable to win her confidence, so that I was unable to discover much about her early

background, except that life in the institution had been pretty grim. As the "colitis" persisted after admission, I think the possibility of the self-administration of abortifacients can be excluded.

I have another case of "colitis" in pregnancy in my hospital file:

CASE 9.—A married woman, aged 23, a small, fluffy blonde, whom newspaper reporters could hardly avoid describing as a girl bride. She was the youngest of 7 children. Her father died when she was 13. Another widowed mother. Her mother, she remembered, use to dose her with syrup of figs as a child. On leaving school she became a maid at a boarding house and married the visiting milkman at 19. They lived at first in rooms near her mother, but 2 years later the milkman bettered himself and installed his wife in a brand new Council house in a garden suburb some miles away from his mother-in-law. Within a few months of the separation my patient developed pain, sickness and diarrhea. This illness invalidated her for 9 months, and had the much desired result of bringing her mother to the rescue, ostensibly to do the housekeeping. She recovered, and all went smoothly for 9 months. Then a relapse set in. She was admitted to my ward 2 months later, and I found on examination that she was 3 months pregnant. I also discovered that she had not told her husband or her mother of the amenorrhea; further, that she was scared stiff about the pregnancy, having heard some realistic descriptions of labor from her young married acquaintance. She began to improve after reassurance, but unfortunately I dieted her rather strictly, as vegetables and fruit increased the secretion of mucus. She developed a pellagra-like condition, with pigmentation, pustular rash, stomatitis and paresthesias. Wallwork, in a discussion at the Cabot Clinic, described a similar sequel during the treatment of a case of ulcerative colitis. She could not tolerate bemax or marmite, and before I could give her more than one dose of liver as a source of vitamin B she aborted. After the miscarriage she rapidly improved.

And now I want to describe another type of case which I think of as the "rolling stone." More accurately, I am thinking of the middle-aged spinster who has never been trained to earn her living, and who, as Barber said of a case of mucous colitis, "remained at home a failure."

CASE 10.—One example I dealt with recently was a lady, aged 57. Since the age of 17 she had always been subject to "attacks" of diarrhea when she was preparing for any special occasion. She started work as a milliner. She had to take it up, she said, but she loathed it, and at the end of 5 years she developed "colitis" and retired from the commercial struggle. Eight years later she was still hoping for a cure, and underwent a curettage, believing she would get some relief. Two years later she was admitted to a London hospital for observation and was discharged with the information that her case was incurable. Having no means of her own, and 4 brothers, all married with young families to support, she attached herself to a wealthy but delicate cousin as a companion, and for 20 years she maintained a roof over her head by adapting herself to the whims of a semi-invalid. This tyrannical old lady did not permit her companion to leave her even when her mother was seriously ill, but graciously extended her a day's leave to go up for the funeral.

Even this bereavement did not provoke a diarrhea, but 9 months later the rich employer had to enter a nursing home for a serious operation. The prognosis of the surgeon was very grave, and so my patient was at last brought face to face with the precarious reality of her existence and

suddenly collapsed with sickness and diarrhea. When admitted, her chief phobia was that the other patients in the ward were going to die, an obvious projection of her terror that her protector was about to perish. She told me that she felt abandoned, that she had no claim on anybody. She made little improvement until the news came that her cousin had survived the operation, had sold her house, and was going to live abroad, and her services, such as they were, would no longer be needed. Her last hope gone, my patient found that when the worst came to the worst, she could face it, and 2 days later she discharged herself, much improved and ready to tackle the world.

CASE 11.—Another patient, aged 66, was the middle child in a family of 5. Always delicate, she never ran about like other children, and was allowed special delicacies on account of her weak stomach. At the age of 17 she developed "colitis" while she was waiting for admission for an operation for strabismus, and passed blood and mucus. She was trained for book-keeping, but she did not like it, and at the end of 5 years gave it up on the pretext that she had to prepare for her marriage which took place a year later. After being married for 20 years her husband left her. Her younger daughter departed to keep house for her father, her elder daughter was married by this time and living in Singapore. Once more she was alone in the great big world; and so she settled down for the next 16 years to a life in London bed-sitting-room, doing unskilled nursing. She gave up this hand-to-mouth existence 4 years ago to come to Bristol to nurse a dying sister. The sister died after 9 weeks and for the next 4 years the patient continued to bolt in and out of boarding houses and convalescent homes wangled from her panel doctors. Having left the metropolitan scene of her labors, she lost her connection, and there was no demand for her services as unskilled nurse in a strange city, and finally when she was sent to me, she had come to the end of her money and resources. She had stayed with all her friends, been to 3 convalescent homes in as many months, and now the "colitis" had begun again. On admission she was Roentgen rayed; the barium meal reached the cecum in good time, but did not progress further than the ascending colon for 48 hours and reached the transverse colon in 96. There was no ptosis but a little diverticulitis. She subsequently survived 10 days without an action of the bowels, without rise of temperature or discomfort. With a technique borne of years of practice she mobilized the good will of the almoner and on discharge had found herself yet another temporary perch.

My last case is another example of the widowed mother-daughter situation:

CASE 12.—The patient was the youngest of a family of 3 girls. The father had died when she was young. This girl was the brains of the family, who saw to it that these were duly exploited. As a librarian, she kept the rest of the family, and was expected, after long hours, to come home and do the greater part of the housework. The mother was perfectly healthy, but the most selfish woman I have ever heard of. I learned nothing of this from the patient, but from her doctor. For 10 years she was the family Cinderella. Then she developed appendicitis, and was operated upon for a perforated appendix. Once the treadmill of service ceased to revolve, it was difficult to start again. The patient made a slow recovery, keeping to her bed for 5 months. She was never able to resume her work, but stayed at home to listen to the interminable regrets of her mother for the days when the family were better off on her salary. The family, anxious to conserve the source of the golden eggs, sent her to this doctor and that in a hope of getting her back to work again, and eventually an enthusiastic surgeon discovered an alleged septic focus in her tonsils and these were

removed. But their hopes were dashed; she developed "colitis." Roentgen rays showed ulceration of the colon; the stools a non-lactose fermenter, and in 8 months she slowly slipped down hill, in spite of blood transfusions, and died. Her mother characteristically kept away from her deathbed, as she found these scenes so "trying."

I have tried to convey to you this short series of cases the psychologic background of "colitis," as I have seen it. The President¹⁰ has already described a case in his paper and C. D. Murray,¹¹ in America, has also published a short article on this question.

I think we can claim that many of these cases begin as an alteration in function of the vegetative nervous system, which selects the colon as the battlefield on which the emotional conflict is fought out. As 1 patient of Bockus¹² said: "The amount of mucus in my bowel is a barometer of my nervous state." I have never been able to satisfy myself in my own cases that there was any organ inferiority in bowels. Many of my patients had a normal bowel without ptosis or kinks, or redundant folds.

Perhaps it is as Larionov,¹³ the Russian artist, said of some paintings produced by artists when serving their term of conscription in the army, "an art of the watercloset," the only place where a soldier could express himself.

I do believe that it is not so much an anatomic organ inferiority in question, but an inferiority of organ function that matters, and that the seeds of "colitis" are probably sown by the strict mother who trains her small child to habits of cleanliness with too much severity, impressing on the child how inferior it is not to be able to regulate its bowel function better.

It is remarkable how so often in these cases the dominant mother has cropped up—particularly the widow, who in the absence of the father has a reinforced authority. On the part of the patient there seems to be a remarkably childish outlook, a submission to the wishes of her parents, a lack of initiative in tackling the problem of earning a living; notice how many of the patients disliked their occupations, and were relieved to escape them by colitis. Of the young unmarried patients, 2 had no interest in the opposite sex, the third had become engaged to a man she must have known the rest of the family would disapprove of.

I have described no men in my series, but Murray had 7 reports in this paper of men who were all tied to their mothers. Though they "felt cramped," they hadn't got the guts to look for a mate.

This was the situation of my older patient, who rather than forge out a career had contented herself with a life of humiliating subservience as a dependent on a mother substitute.

I believe that "colitis" is often the somatic expression of the emotional conflict between the reality, "You must grow up," and the phantasy, "I want to retain my childish dependence on my mother."

The beginning of "colitis" is a "psychogenic mucorrhea,"¹⁴ determined by an "overdependence on the parental love and shelter"¹⁵ and often aggravated by the death of the father.

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THE COMMON DENOMINATOR OF DISEASE.*

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THE common denominator of all human diseases is a variant represented by the individual person within the patient. The factor which is generally designated "etiologic agent," also a variable, might then be viewed as the numerator. From this standpoint there can be no doubt that physicochemical energy represented, for example, by the activity of the meningococcus alone is not meningitis, nor is the effect of the metal lead *per se* equivalent to anemia and colic. The principle, likewise, holds for energy expressed in terms of emotion which, at present, is classed in the world of imponderables. Consequently, it may fairly be said that the result of

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fear alone is neither hyperthyroidism nor peptic ulcer. As a corollary to this proposition, one may state that the coördinates, meningococcus, lead and fear, are not the cause but rather part causes, respectively, of meningitis, plumbism and peptic ulcer. For the incidence, intensity and variation in the clinical picture of these three pathologic reactions is determined in large, yet ever-changing, measure by the other necessary factor, namely, the essential quality of the affected individual.

If we accept this ancient thesis, then, as physicians we are obligated to inquire into the nature of the man as precisely as we now do into the destructive agents which beset him. In the past this was done by the best clinicians in purely empirical fashion. The great doctors of earlier days had an uncanny "feeling" for the man within the patient, an intuitive perception of his special nature. But this sixth medical sense has been well nigh impossible to transmit to students, nor could it be crystallized in any sort of valid formula. Consequently, coincident with the effort in recent years to establish truth by mathematics, it has been to some extent neglected.

Now there are two important questions which at present confront clinical medicine, namely: Whether or not the doctor's understanding of the human animal as a total living organism is adequate; and whether or not this knowledge, so necessary to the clinician, can be moved from the sphere of empiricism to that of science.

At the Constitution Clinic in the Presbyterian Hospital we have approached these questions from the point of view which organismal biologists entertain toward any living creature, be it ameba, sea anemone or the larvæ of amblystoma. The work of the earlier medical natural historians, Hippocrates,¹ Aristotle,² Linnæus,³ and that of the later group, Jacques Loeb,⁴ Ritter,⁵ Conklin,⁶ Morgan,⁷ Vogt,⁸ Spemann,⁹ Coghill,¹⁰ and Cannon,¹¹ has pointed the way. (1) They have queried, What is the creature's appearance, and (2) How does it behave?

But to be a student simply of the person within the patient is always a difficult task for the physicians and sometimes an impossible one. When an acutely ill man appeals for relief, swift examination of the nature of the malady and prompt treatment is the first obligation. Furthermore, the symptoms and signs of the pathological process strike so forcibly upon the senses that they obscure the individual behind them. It is likewise in general true, except perhaps in the sphere of infection, that as somatic change waxes with chronicity, tests by physical and chemical methods become increasingly spectacular. Such hazards to direct observation of the person which lie in the clinician's path, however, do not exist, as MacKenzie¹² pointed out, to the same degree when the sick man is seen at the very start of his malady. At such a time the so-called "ravages of disease" have not yet distorted the appear-

ance and conduct of the human organism's "total personality." The physician may still view him as an organismal entity. Yet even the destructive influence of prolonged illness never quite obliterates the strange quality or flavor of the man within the patient. This personal specificity is highly durable and to the end stubbornly resists destruction. It is illustrated, for example, by the discovery that grafted tissues never lose their specificity; or by Wheeler's¹³ observation, that ants, enclosed in amber from an epoch 2,000,000 years in the past can be identified with forms which crawl today.

The principle also appears in history in the persistence of the Hapsburg lip and the Bach family's musical gift. In the clinic or general practice, physicians are familiar with the persistence of the original personality. One has only to remind the reader of the tall slender youth, with dark coloring and silent aloof demeanor who does not mix well with his fellows at school. Some years later the shadow of that boy may be glimpsed in the sullen paranoid or rigid close-bent catatonic schizophrenic.

In the sphere of so-called bodily disease a similar picture might be drawn of the large, deep-chested, heavy youth, with very broad, short face, whose blue eyes are set far apart and whose pink cheeks and exceptionally fine, silky hair are the joy and pride of his mother. Yet his rather neutral, gentle, fireless disposition somewhat disappoints her. Many years later, she or the old family doctor sees the shadow of that florid youth beneath the light, tawny skin, soft, flaccid tissues, and pale, lusterless blue eyes of the patient with pernicious anemia.

And so it would seem that as change proceeds in somatic tissues, both functional and structural, modification of the animal's original character ensues. Yet no matter how greatly this individuality be distorted by advancing disease, its essential quality is never obliterated. It seems to be the most tenacious quality of living creatures, imperishable in the individual so long as the race survives, yet far less well explained than are many of the detailed processes which, acting together, subserve the biologic purpose of the living organism. In commenting on these matters, Jacques Loeb writes: "The definiteness and constancy of each species must be determined by something equally definite and constant in the egg, since in the latter the species is already fixed irrevocably."

Yet while this species constancy is fixed in the egg, the organism reacts quite differently to external stimuli at different stages of the growth and development. These differences seem to depend upon the successive addition of parts which are necessary to the finished whole. Thus Murphy¹⁴ showed that foreign tissue was accepted by and would grow in the chick embryo before the twenty-first day, when spleen and lymphatic tissue appeared. After that stage, evidently related to some change in the whole embryo produced

with the addition of lymphatic substance, foreign tissue was rejected. The observations of Stockard¹⁵ on trout embryo showed that the different viscera appeared at definite times in the developmental process, each new budding organ holding what he called a "moment of supremacy." But though it would seem from these experiments that the parts were in a sense directive of the whole, the more recent studies of Coghill¹⁰ upon amblystoma embryos indicate the reverse. "In like manner," he writes, "the tissues of the tongue receive branches from motor neurones that are engaged in integrating the trunk long before the tongue has muscle tissue in it. It is, therefore, the potentiality of the functional neurone to grow in embryonic fashion that gives to the organism as a whole its ability to subjugate new parts and thereby maintain its unity during the development of behavior. Such growth of the already conduction neurones accomplishes, then, the primary function of the nervous system: the maintenance of the integrity of the individual while the behavior pattern expands."

This statement expresses well the notion that whatever may be the purpose behind the "definiteness and constancy of each species," at least it results in the fact that all the processes in the growing and developing embryo and young animal move toward the eventual production of a finished whole—a complete organism to which each part is subservient. For the clinician the organismal concept may be more significant than is at present generally accepted. There has been so much detailed information about individual organs obtained during the past decade by highly specialized methods that these have naturally become the focal points of medical interest. As I have recently stated: "The difficulty, however, with this sort of knowledge of human beings is that the skeleton, the muscles, or the organs are only those and quite useless until each and all combine and function smoothly together in the service of some particular person."¹⁶

The student of human constitution, or clinical organismalism, would have an easier task if man's reactions to environment were, like those of an ameba or earthworm, limited to physical nature. So far as we know, the life conduct of those forms expresses simple reflex response to direct physical and chemical stimuli. Consequently, the interaction between the living organism and its special environment at that level is less difficult to observe and interpret than is so in man. In his case the creature himself is infinitely complicated and dwells, furthermore, at one and the same time in two separate and complete worlds, those of reality and phantasy. Indeed, it is often impossible to determine which one supplies the adverse stimulus, or "external agent" of his illness. It becomes necessary, therefore, to investigate the zone wherein the human organism's envelope, physical and psychologic, merges with its special environment. Such inquiries should properly cover every

stage of the individual's growth and development and include each detail of conscious memory and as much of the hidden content of the subconscious as can be retrieved by adequate psychologic technique. Thus it is apparent that the study of the man within the patient actually becomes the study of the "man-environment unit." Fig. 1 presents the idea in diagrammatic form.

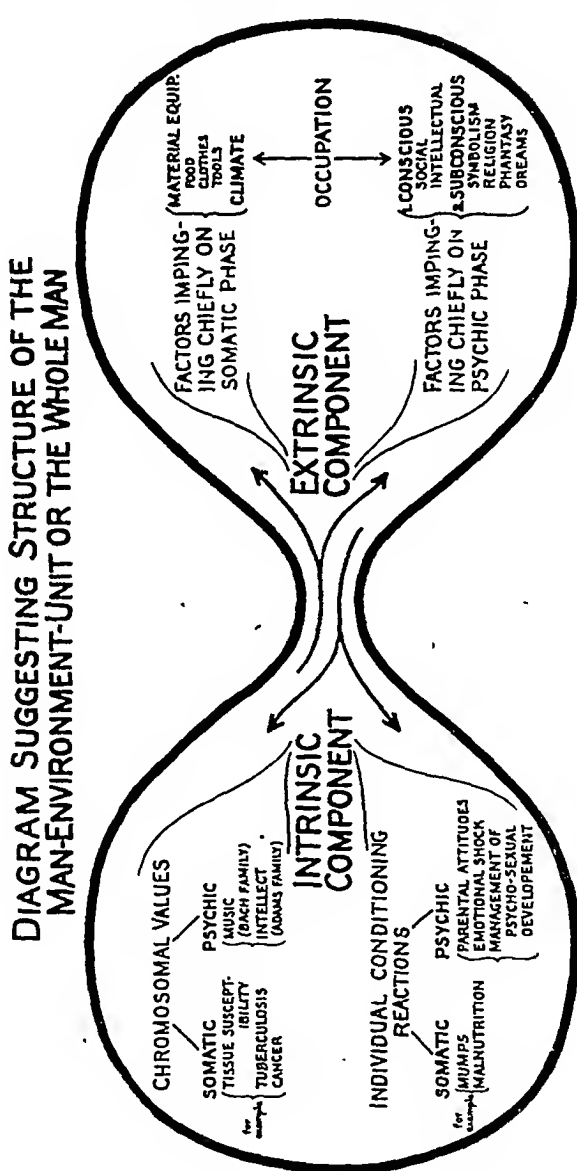


FIG. 1.—Note the arrows representing the flux of interacting forces which form the continuity between living organisms and their individual environments. (From New York State J. Med., 34, 11, 1934.)

The main problem, however, which confronts the clinical organismalist, or student of human constitution in relation to disease, is to be able to evaluate correctly the man or woman whose disease he is called upon to cure. For the moment let us fix our attention upon the man himself as a specific part cause of his own malady.

Like every living organism there are two phases of his being to be considered. The first of these is his form and size, which are the end results of growth and development. These in turn rest upon inherited and conditioning influences. The bones, joints and skeletal muscles combine to enable the animal to negotiate successfully, under the direction of the psychophysiologic command, such time-space relationships as are necessary to its wellbeing. Second, we have to investigate that far more complex and obscure combination of viscera which control the inner life of existence and procreation. The main elements in this extraordinary phase of the human being can be designated as cortex, thalamus and hypothalamus, autonomic nervous system, endocrine glands and smooth muscles. This complicated system will hereafter be referred to as the corticohypothalamus mechanism. These are the physical, structural units, but there is still another factor which is difficult to place, yet which seems to direct the whole—namely, emotion. The scope and purpose of this communication, however, does not permit full discussion of the psychology of emotion. But because the matter is one of such great significance in the problems of internal medicine, and especially because the quality and intensity of emotion and its effects upon physiologic processes is so specific and variable among human beings, it is necessary to deal with it as an essential element of the total organism.

For a good many years the theories of emotion advanced by James and Lange¹⁷ were accepted as final. They were so nearly alike that their tenets have usually been spoken of together, as the James-Lange theory. As Cannon states briefly: "These observers believed that the chief point of the felt emotion depended on the visceral and organic part of the expression." But with new methods to assist him, together with supporting observations from the surgical findings of Cushing,¹⁸ W. B. Cannon reached a much more satisfactory idea of the nature and source of emotion.

Fig. 2 shows in diagrammatic form Cannon's thalamic theory of emotion, with the addition of a plan to link the mechanism of repressed or forgotten memories and symbolic stimuli to the whole. This supplement seemed to be desirable from the clinical standpoint for there can no longer be doubt that the emotional patterns, buried deep in the subconscious mind, are capable of producing changes in physiologic function. Indeed, even before Freud, there were many indications in the literature from earliest folklore to the writings of Schopenhauer and of Nietzsche that men recognized this fact. And so it seems probable that by lifting the thalamus into the surprising position it now holds in the apparatus of emotion, Cannon has gone far to unite the work of internist and psychiatrist.

If we now turn to the problem of applying the organismal point of view to the clinic we are immediately faced, as in all other scientific research, with the question of methods. In general, these fall

into two classes: (1) Those which are applicable to the body structure, or architecture; (2) those which relate to organic function and conduct of the individual as a whole. Direct observation by

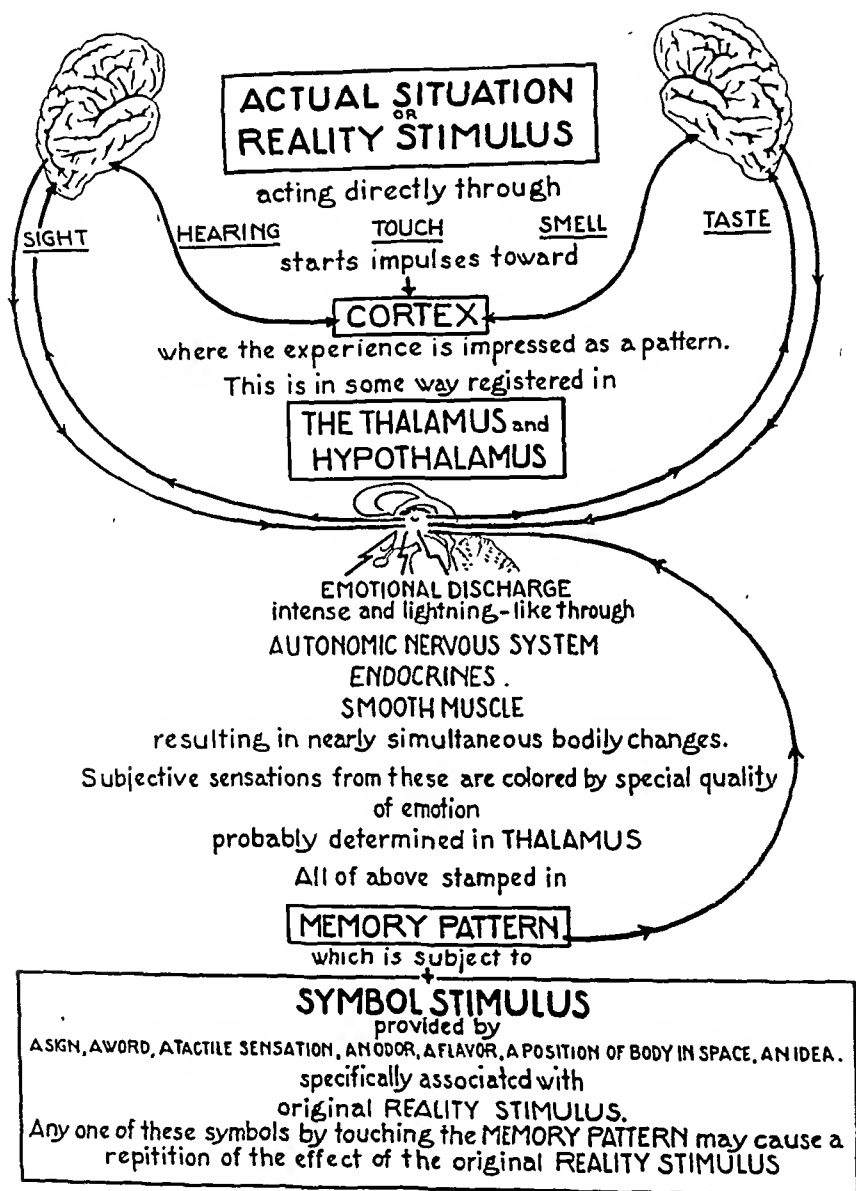


DIAGRAM OF CANNON'S THEORY OF EMOTION

FIG. 2.—Diagram of Cannon's theory of emotion with addition of memory mechanism and symbol stimulus.

inspection is still perhaps the most valuable means of studying the morphology. Anthropometry, which we have used greatly in the past, probably does not contribute as much as one would demand

from a precise method. It is helpful but does not supply as much information as can be gained from the non-measurable characteristics. The contours formed by soft tissues (muscle and fat), the shape and position of eyes; form, position and quality of teeth; texture and color of skin and hair and the latter's distribution; pigmentation and hyperextensibility of joints; and, finally, the design and size of external genitalia; all these are not measurable characters, yet they usually tell far more about the individual than do measurements. They are the characters which are so grossly modified in the fully developed stages of many well-known endocrinopathies and have been successfully used as aids in endocrinologic diagnosis. Indeed, the slight differences in form, tissue quality, fat distribution, color, which stamp individuality upon a man, may properly be referred to a well-recognized endocrinopathy as to a yardstick.

The first 2 cases to be presented illustrate two phases of the morphology problem. In 1 example the presenting malady is perhaps chiefly foreordained through some genetic fault in the germ plasm. At least no external exciting part cause can be discovered. In the second, the final pathologic situation results in part from the conditioning effects of an infection during the growth period of the organism. But the organism exhibited the developmental fault of cryptorchidism.

CASE 1.—G. H., a cabinetmaker, male, aged 48, complained of weakness, depression, dyspnea on exertion, malaise, numbness of fingers for past 2 years and some pain and heaviness in frontal region. He tells his story in a very soft, gentle, though low-pitched, voice. His expression is not animated and suggests the unemotional, resigned acceptance of life so often seen in gentle, elderly women. This look is rendered more poignant by the delicate wax-colored skin, which is profusely crinkled by very fine lines, like crushed tissue paper. There is scant and spottily distributed hair on the face, which the patient states he has never needed to shave more than twice a week. The teeth are unusually small and there is a wide separation between the central incisors.

Heavy shoulders and a deep, short chest give a first impression of virility, which is supported by apparently large external genitalia. But the rounded contours of the shoulders, trunk, abdomen and hips throw the emphasis more toward a feminine form. Furthermore, though the scrotum is long and rather redundant, the testicles are not large and they can be easily caused to disappear entirely in the inguinal canal. When it is pushed well up, the right testis will remain concealed indefinitely until pushed down again.

The morphologic picture was one which could be compared with the eunuchoid yardstick and represented what may perhaps be called the neuter, or species, type. Further evidence of the reduced virility was the almost complete absence of hair from trunk and extremities. The pubic mass was sharply circumscribed. But the patient's hands struck sharply across the otherwise eunuchoidal conformation. They were very large, thick-set and stubby, with large flat nails. The hands alone could be compared with the yardstick of acromegaly. But this was again belied by the delicate modelling of nose and chin. Only the separated incisors agreed.

In the functional sphere this patient showed, as Cushing pointed out in

1912, that "In many of the cases in which hypopituitarism is the striking feature, traces at least of an early tendency to hyperpituitarism can be detected." This man in early manhood was exceptionally powerful and excelled his fellows in feats of strength (see Cushing,¹⁸ Case 1). In the psychosexual field, likewise, this patient's history revealed a double fluctuation. Thus in his earlier years his libido was laggard, for 2 years after marriage it became exceedingly active, then waned slowly, until 18 months ago, when it disappeared entirely.

On the basis of the total personality, some maladjustment between pituitary and gonad was suspected, and because of the hand conformation and the teeth, attention was chiefly drawn to the pituitary. A radiograph of the skull revealed a large tumor which had nearly destroyed the posterior portion of the sella. There were no neighborhood symptoms.

The detailed description of the personality has not been given to demonstrate the effect on symptoms and signs of the tumor's presence, but rather to promote the notion that the man's constitution is a coordinate of the tumor. This total organism was destined to be unsuccessful. From the start the forces which determined its somatic and psychic characters invited the tumor; they did not result from it. The tumor in that sense inevitably becomes part of an originally faulty whole. One might almost say, "The man is in part the tumor," instead of the customary, "this man has a tumor."

CASE 2.—This patient (reported previously as Case 3, p. 123, *Disease and the Man*, 1930) falls in a category somewhat similar to the first. From the organismal standpoint there were two significant aspects of this man's total personality: (1) As a member of a large clan which showed a strong factor for shortness, he became an outstanding variant in the matter of length growth. (2) The quality of his personality and whole life adjustment were profoundly modified from the expected family pattern by the developmental fault—unilateral cryptorchidism—on the one hand, and the special conditioning accident of unilateral castration by mumps on the other.

The preceding 2 cases were presented to illustrate the importance to clinical medicine of direct observation of the structural plan of a given human being. The following case is offered in demonstration of the difficulties and possibilities of approach to the functional plan of a given individual. It is in this sphere that synthesis of existing knowledge of autonomic nervous system, endocrinology, Cannon's thalamic theory of emotion and psychoanalysis are of first importance.

CASE 3.—An American of Scotch origin, aged 36, a professor, married and has 2 children, girl and boy. He is 6 feet tall, slender, well coordinated and moves with swift easy stride and gesture. His hair is tawny, the skin white, delicate and freckled. His vivid blue-green eyes convey the notes of curiosity, comprehension, fear, cruelty and merriment.

The zygomatic facial zone is broad, interpupillary space 64 mm. (above average of 60 to 61); the cheek zone tapers sharply to a pointed chin. The nose is narrow and acute. The thin compressed lips form a mouth line which is straight and severe. Thus the face is a clear portent of the pattern of his psychic panel: high intellect, unyielding determination, extraordinary sensitiveness, fine feeling and subtle humor. The pace and tension of the entire organism is extreme.

Routine physical examination at the first visit, 7 years ago, disclosed no pathologic structural changes. The heart rate, surprisingly for so tense a person, was 66 even under examination. The blood pressure was 120/80.

There are 3 major symptom phases in his patient's recent medical history. They involve 3 so-called main systems of the total organism—digestive, circulatory, ideational. Since March, 1927, when he first sought relief, the emphasis upon symptoms in each system has had a certain chronologic sequence. But in the entire life story, from the first there appear evidences of disturbance now in 1, now in another of the 3.

1. *Digestive Phase.* At the first visit, in March, 1927, the patient told of 3 similar attacks of terrific abdominal pain, which doubled him up—lasted 12 to 30 hours and left him completely prostrated. As the pain abated he would fall asleep, then awaken suddenly feeling weak and ravenously hungry. A curious and, as it later turned out, most important feature of the hunger was a specific craving for baked beans.

The 4 diagnoses which had been made were: gall stones, perforated peptic ulcer, acute pancreatitis and kidney stone. Physicians who examined him during the attack found no point of especial tenderness but a board-like abdominal wall. In 1 instance preparations for immediate laparotomy were made. The patient objected and instead was given morphin.

Careful questioning revealed that in one instance, for some reason quite unknown to his conscious thinking, he had eagerly read in the newspapers every detail of the last illness of the moving-picture actor, Rudolph Valentino. Two to 3 hours after hearing of Valentino's death the severe attack of pain began. Following the lead of this association, the patient remembered that each one of the other attacks had followed upon hearing or reading of a person who had died of appendicitis or acute general peritonitis. This discovery led, in turn, to the memory of his terror on hearing, at the age of 10, how a friend of his father's died in agony of that disease. From that recollection his thought moved rapidly backward in time to his own nearly fatal illness, cholera infantum, at the age of 2½. This experience had often been recounted to him by his mother, who clung tenaciously to each gruesome detail—how he had writhed in pain, how terrifically his bowels had moved, how she had massaged his tiny, shrunken limbs back to life and how, finally, when he was permitted the first solid food she had given him baked beans which he had ravenously devoured.

For brevity's sake, report of the routine medical tests, which were all negative, will be omitted. The behavior of the stomach, however, is of interest. Following a bismuth draught the stomach was observed first at rest as the fluid entered and then under massage. When this mechanically provoked peristalsis had subsided and the stomach was again quiescent, I leaned down in the dark and whispered in the patient's ear the words, "Rudolph Valentino died of peritonitis." Almost immediately the stomach could be seen to move and soon was again in violent peristalsis. In conscious response to the whispered sentence he laughed and asked if I were "kidding him." Then about 30 seconds to 1 minute later he said, "My God, Doctor, that bismuth must be disagreeing with me, I've got some cramps coming on." (Note delay of subjective sensation.)

This Roentgen ray experience aroused the patient's interest in the emotional origin of his abdominal attacks, and during the next few months he brought in reports of other early memories of digestive upsets, especially of sudden unexplained diarrhea and his mother's great solicitude about them. It appeared that much of his childhood memory centered about her continual concern whether his bowels were moving too little or too much. It should be mentioned at this point that when the patient was 5 years of age his father had died following an operation for gastric ulcer. This experience terrified him, but not so much, he said, as the one when at the age of 3 his father, a great, powerful, bearded man, had carried him on his shoulder into the ocean surf. The waves had broken over him and he felt the pangs of suffocation.

During the next 4 months there were about 20 conferences in which disclosures, germane to the other 2 system disturbances were made. The patient, who is a professor, noticed an increasing difficulty in meeting his classes, feared their criticism and was embarrassed to the point of physical distress, trembling, sweating, palpitation, nausea, weakness and diarrhea.

In discussing the symptom of palpitation it came out that about 7 years before the patient had consulted a doctor in the West who was a large man with a very deep loud voice. During the interview the doctor "looked at me as though I were a convict and asked me if I ever had pains in my stomach. Then he took my blood pressure and said 'My God man, it's 190. Go home—don't walk—take a taxi—and go to bed at once.' I was terrified."

At the close of the 4 months of conferences the patient went away and was not heard from again for 5 years. When he reappeared he complained of attacks of weakness, referred to his heart.

2. *Circulatory Phase.* On November 30, 1932, he reported having been very well, entirely free from abdominal cramps and had held his weight. Now he complains of elevation of blood pressure and fear of stroke. He has been refused standard premium rates by life insurance companies on account of his continued increased arterial tension. His mother has high blood pressure and lately 2 of his friends have suffered strokes.

Examination revealed the blood pressure 160/80 in recumbent position and a very loud pistol-shot sound in the artery. The pressure rose 10 points within a few seconds when I asked for the name of a friend who died of stroke. But on repeated subsequent readings it did not fall below 160. There is sinus arrhythmia and marked slowing on deep held inspiration. The heart is not enlarged. Routine urinalysis and blood chemistry gave normal pictures.

Because he now no longer lived in New York, strict psychoanalytic technique was impracticable. But after 14 months of irregular conferences the blood pressure gradually sank to 130, where it has remained. He now pays regular life insurance rates. But as the blood pressure fell, symptoms of anxiety increased.

The first intimation of the ideational phase was suggested by the rather remarkable statement that: "Blood pressure is to me a concept very subtle and powerful like God; like the flashes of lightning and thunder on distant mountains; something way beyond the power of man's volition to cope with; and emphasizes man's inability to do anything about God, who was the ultimate judge on matters of sex and he had decreed that intercourse was sin."

The sense of being overwhelmed, he said, reminded him of being nearly drowned in a swimming tank when he was 10 years of age, when thrown in by a big bully, and also of the time when his father had held him in the breakers at the age of 3, petrified with fear.

3. *Ideational Phase.* At first the phobia was limited to his circulatory system: death from a stroke or heart failure from high blood pressure. These ideas in turn resolved, first, into fear of suicide, and then the more terrifying thought that he might kill his children, his wife, his mother, the doctor, or anyone he met. The mental anguish occasioned by these phobias was almost unendurable. Following each wave of homicidal fear, the patient experienced the sense of collapse and complete disintegration, which he had previously connected with his heart. The symptoms of exhaustion, palpitation, leaky skin and trembling resembled the picture of hyperinsulinism so closely that it seemed desirable to make observations upon the patient's blood-sugar curve before and after a normal meal, but with normal results.

Space does not permit a full account of the psychoanalysis. But there is

ample evidence to show the serious effect upon the patient of the birth trauma, the great sense of inferiority due to his spindle legs and very small genitalia, the strong homosexual trend, arising in the wish to be subjugated by the father, and the fear (or wish) for castration as a solution of the masturbation guilt, and the oedipus situation. Indeed, the fear that masturbation history would be discovered caused this highly intelligent and educated adult to delay 5 years in finally returning to complete his analysis.

Following the resumption of the conferences the analysis went along smoothly and with comparatively little resistance. From this time on he continued to improve, and at present (May, 1935) he is entirely free from abdominal cramps, his blood pressure is normal and the phobias are reduced to occasional slight and transient reverberations. The case shows clearly that because of the same emotional patterns underlying all the symptoms the patient was not cured when the original cramps disappeared 7 years ago, nor when the blood pressure fell to normal last May. He can be regarded as finally cured only when, in addition to the removal of these two system disturbances, the phobias likewise vanish.

These cases have been selected from a large material at the Constitution Clinic for the purpose of illustrating differences between the persons within the patients. The first 2 provide instances of the situation in which the somatic component (somatic in the sense of structure, architecture, morphology) is the more emphatic criterion of the personality. The third displays a form in which the psychic component (psychic in the sense of corticothalamic mechanism, functional, emotional) predominates. The individual quality (constitution) in the former, in general, results from genetic and conditioned faults in growth and development, and contributes to the production of diseases involving those parts of the body which are concerned with the animal's outward or spatial environmental relationships. In this category, for example, are found diseases of bone, joints, skeletal muscles, motor nerves and weight loss or increase. The individual quality (constitution) in the second group in general springs from genetic and conditioned faults in the corticothalamic mechanism and contributes to the production of those diseases involving vital functions supporting the inner life of existence and procreation. Hyperthyroidism, peptic ulcer, Raynaud's disease, asthma and some forms of arterial hypertension may be given as examples of maladies common to the second category. But these two phases or groups must remain very loose ones, for the obvious reason that functionless structure serves no biologic purpose and function cannot be realized without structure.

Now what significance may the foregoing observations hold for therapeutics? It brings us face to face with the question of why or how psychotherapy in some form or other has since time out of mind been one of the most potent agents in the cure of sick people. Clearly, in the first 2 cases with profound structural fault we are at present powerless to do more than to relieve subjective suffering. Probably therapeutic success in the true sense of cure bears an

inverse ratio to the degree and duration of somatic change. But in the last case structural tissue change had not yet advanced to any degree notwithstanding the extreme severity of the symptoms.

I have used Cannon's theory of emotion for the basis of the chart (Fig. 2), and added the lower part about memory patterns to emphasize the importance of symbolism for mankind. It is perhaps not too much to say that if reality situations and memory patterns are capable of causing function-modifying and tissue-changing emotional discharges from the thalamus, appropriate psychotherapy, interpreting and applying individual and racial symbolism effectively may tend reciprocally to remove the destructive patterns by a process of unconditioning. Recently the surgeons have advocated the use of operations which involve removal of portions of the autonomic nervous system or certain endocrines. No doubt there is a point in the advancing process which moves from early functional disturbance to actual tissue change, at which removal of hypertrophied tissue or blocking the channels through which it acts by surgery is the only effective treatment. But we must weigh carefully the relative merits of a therapy which "cures" (*i. e.*, reduces symptoms) by destroying the integrity of the whole and a therapy which by reintegration of the personality restores an adequate balance of the corticothalamic mechanism. But the latter in turn is limited by the quality or constitution of the individual.

Conclusions. 1. The common denominator of human disease is the individual man or woman—the specific total organism—within the patient.

2. The specificity of that organism as part cause of the presenting disease is analogous to the specificity of the exciting agent from environment.

3. The layer at which the organismal envelope and its environment meet is not sharply drawn. The two may be continuous in a physicochemical sense.

4. The fact that man occupies and reacts with two complete universes—reality and phantasy—renders each disease condition doubly complex.

5. The specific quality of individual human organisms is determined largely by the quality and relationships of the 5 structural parts: (1) Cortex, (2) thalamus, (3) endocrine glands, (4) autonomic nervous system, (5) involuntary muscle.

6. Much information about these can be gained by direct observation of form and function of the organism as a whole—amplified by information concerning its various stages of growth and development.

7. Since any living organism is a link in an hereditary stream of special racial and family protoplasm, genetic histories may contribute to the doctor's understanding of the person within the patient.

8. Because man is a complete psychosomatic being, studies of

his psychologic structure are at least of equal importance to internal medicine as are those of the soma. It is possible that what we now term the subconscious is actually composed of memory patterns in the corticothalamus mechanism. This complex carries not only inherited qualities but also phylogenetic and ontogenetic conditioning effects.

9. The studies of internal medicine deal especially with the later purely somatic resultants of the whole disease process and consequently are often concerned with phenomena widely separated from the initial disturbance. This in many instances can be shown (by means of a meticulous history of the person's physical growth and development and of his emotional reactions, both conscious and unconscious) to arise in an early disturbance at the psychophysiological border. Consequently it is at this point that the sphere of psychiatry (psychoanalysis) relates directly with that of internal medicine.

10. Cannon's theory of emotion and the added memory mechanism indicate how important it is for the physician to search for the specific symbol stimulus. This may require deep psychologic technique, for often the original reality stimulus is lost to conscious recollection.

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BOOK REVIEWS AND NOTICES

CLINICAL TUBERCULOSIS, in two Volumes. Edited by BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois College of Medicine; Honorary Professor of Medicine, National University of Mexico; formerly Director of the City of Chicago Municipal Tuberculosis Sanitarium. With the Collaboration of 33 Contributors. Pp. 1580; 640 illustrations and 9 color plates. Philadelphia: F. A. Davis Company, 1935. Price, \$22.00.

THIRTY-FOUR contributors have produced a very creditable work that presents all the clinical phases of tuberculosis with sufficient completeness and detail to deserve the term "encyclopedia." The text is divided into 13 sections, designated by the letters A to M: unfortunately, each section has its page numbers begin at 1, with the section letter preceding it, a cumbersome and unnecessary procedure. Section A includes chapters on epidemiology, bacteriology, allergic and immunologic considerations, pathology and pathologic physiology of the tuberculous lung. This section is particularly well done. Section B deals with diagnosis, classification of pulmonary tuberculosis, Roentgen-ray findings in adult pulmonary tuberculosis and differential diagnosis. The chapter on physical diagnosis in some respects is rather skimpy. The productions of roentgenograms are only fair and the chapter on Roentgen diagnosis is the only major chapter without references to the literature. Section C and part of Section D, dealing with prognosis and treatment, including the usual hygienic measures and pneumothorax, pneumolysis and oleothorax, conclude Volume I; they are very well done. Volume II takes up surgical apical collapse, thoracoplasty, heliotherapy, tuberculin and climate treatment, tuberculosis in childhood, tuberculous meningitis, miliary tuberculosis, spontaneous pneumothorax, tuberculosis of pleura, intestines, anorectal region, peritoneum, urogenital tract, special sense organs, cardiovascular system, skin, bones and joints, thyroid. There are also chapters on bronchoscopy in the tuberculous, tuberculosis and pregnancy, diabetes, trauma with regard to industrial and compensation considerations, psychopathology. In spite of the numerous contributors there has been surprisingly little duplication and only one omission which the Reviewer discovered: tuberculosis of the adrenals (Addison's disease). The Editor is to be congratulated on his publication.

R. K.

THE STORY OF MEDICINE IN THE MIDDLE AGES. By DAVID RIESMAN, M.D. Sc. D., Professor of the History of Medicine and Professor Emeritus of Clinical Medicine, University of Pennsylvania; Member, History of Science Society and Medieval Academy of America. Pp. 402; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, \$5.00.

THE Middle Ages have so long been loosely regarded as the quintessence of intellectual stagnation that it is refreshing to be given two more refutations of this outworn *cliché*. Just as Dr. Riesman's book with its background of general medieval university life and customs makes this amply apparent, so does Morison's "Founding of Harvard College" with its generous treatment of the medieval universities and their activities, without which none of the older American universities can be properly understood. As Dr.

Riesman points out in his Preface "the people who produced the Great Cathedrals, the French Chansons, the German Minnelieder, the Magna Charta, Parliamentary Government and above everything, the Universities (and one might add, Hospitals), deserve our gratitude and admiration." Beginning with the Greek inheritance, the School of Salerno, Arabian Medicine and medieval Jewish physicians, the ever changing medical stream is followed in the first third of the book through clerical and scholastic medicine, astrology and alchemy to the six leading universities of the period—two each in France, Italy and England. Far outgrown as the volume is from its original destination as a unit of the *Clio Medica* series, yet one cannot but regret that the universities—a most interesting and important phase of medieval life—could not have even more complete treatment. From a second point of view, such subjects are then treated as anatomy, surgery, the guilds, medieval diseases and epidemics, treatment, hospitals, and medical textbooks. Paracelsus alone is distinguished by a chapter to himself. The vexed question of the origin of European syphilis is presented thoroughly and impartially. As was to be expected, a verdict of non-proven had to be given for the views of both Americanists and anti-Americanists. One finishes this really very interesting and instructive volume with satisfaction in the reflection that a busy consultant should have acquired such a store of historical knowledge and have had the ability and given the time and care necessary to present in such an attractive form. E. K.

A BIBLIOGRAPHY OF THE POEM SYPHILIS SIVE MORBUS GALLICUS, by GIROLAMO FRACASTORO OF VERONA. By LEONA BAUMGARTNER and JOHN F. FULTON. Pp. 157; 9 illustrations. New Haven: Yale University Press, 1935. Price, \$5.00.

THIS bibliography of Fracastoro's justly celebrated poem follows, appropriately, close on the heels of the appearance of the one-hundredth printing of the poem (*AM. J. MED. SCI.*, 189, 864, 1935). Only the *Regimen Sanitatis* of the School of Salernum, among medical poems, surpasses or even equals this record, though its intrepid bibliographer of our day has, alas, yet to appear.

Following a characteristic introduction by Dr. Arnold Klebs, the present bibliography lists the editions by languages, Latin (42), Italian (29), English (13), French (9), German (5), Spanish and Portuguese (one each). These include the usual appearances in collected works and anthologies, which, in some instances, enjoyed more than a single edition. A number of editions represented by unique or very few copies, and consequently generally unknown, are here brought to attention—one of the more obvious fruits of such a bibliography.

The 68 holding libraries recorded are not indexed as regards the individual sums of their holdings, but it is possible to discover that the owners of the largest number of editions are, first, Dr. Fulton himself, and, second, the British Museum. Among the American public or semi-public libraries, the chief holders appear to be, in order, the three largest medical libraries, those of the Surgeon-General, the New York Academy of Medicine, and the College of Physicians of Philadelphia.

The description of the editions is, however, happily far more than merely statistical. The notes on typography, printers, translators, editors, and owners invite the pleasurable dalliance of bibliophiles generally; and it may be presumed that every peruser of *Antiquariatskatalogen* will henceforth find the work, as indispensable for reference as Keynes' bibliography of Harvey or Dr. Fulton's own bibliography of Robert Boyle. It contains, also, a valuable section devoted to biographical and critical material on Fracastoro and his work.

In its general appearance, the book, involving complicated problems in typography, reflects unusual credit upon the ingenuity and taste of the authors and their printers. The world of scholarship, and particularly that section of it concerned with the history of medicine, owes a great debt to the authors for this humanistic bibliography of one of the brightest ornaments of medical *belles lettres*. W. McD. 2p.

THE WOMAN ASKS THE DOCTOR. By EMIL NOVAK, M.D., F.A.C.S., HONORARY D.Sc. (DUBLIN), Associate in Gynecology, Johns Hopkins Medical School; Former Vice-President American Gynecological Society. Pp. 189. Baltimore: The Williams & Wilkins Company, 1935. Price, \$1.50.

THOUGH recognizing the latent danger in a little knowledge, the author offers this discussion of those problems in which all women are interested, much as a gynecologist would answer the questions put to him by an intelligent patient. Especially interesting are the opening chapters on "What is Femaleness"—a very modern subject—and "Superstition and Folk-lore of Menstruation." Other topics cover the anatomy and function of female organs at various stages of life, and a few disorders such as dysmenorrhea, sterility, leucorrhea and cancer. One is inclined to agree that the danger of a woman attempting to use knowledge gained by reading such a book as a basis of self-treatment is indeed slight. E. K.

CLINICAL MANAGEMENT OF SYPHILIS. By ALVIN RUSSELL HARNES, M.D., Chief of Congenital Luetic Clinic, New York Hospital. Pp. 71; illustrated. New York: The Macmillan Company, 1935. Price, \$1.50.

THIS booklet of less than one hundred pages is an effort to render specific, within a very brief compass and at little expense, the technique of the treatment of syphilis, too often only vaguely grasped in the abstract.

The idea is a laudable one but unfortunately its fulfillment in this work leaves much to be desired. Valuable space is wasted on extraneous and unimportant matters, instructions while apparently detailed frequently lack important points and have a sketchy quality not entirely compensated by the efforts at tabulation. For a work dated 1935 to completely overlook the notable American and international contributions to the technique of early and latent syphilis is a grave omission. Sharp exception could be taken to a number of statements and the thing, at least as rendered in words (see p. 18) is at times almost embarrassingly naive. The illustrations are of course drawn to save expense, but have unfortunately lost all their teaching value in the process.

A second edition of this manual will doubtless be called for and an elimination of diffuse material and closer attention to the established landmarks in the recent literature will greatly increase the value of this very useful work. J. S.

THE DOCTOR'S BILL. By HUGH CABOT. With an Introduction by A. LAWRENCE LOWELL. Pp. 313. New York: Columbia University Press, 1935. Price, \$3.00.

THIS volume adds another point of view to the rapidly growing literature on the subject of the economic side of medical practice. Its structure is logical and the discussions are fairly impartial but wholly critical.

The author first presents the contrast of medical education and prac-

tice in the decade or so before the present century and the education and practice of the present time. He strips the old practitioner of much of his romance and glamor but on the other hand seems to overemphasize the importance of the use of laboratory procedures in the practice of today.

Dr. Cabot then proceeds to set forth the fundamental axioms and corollaries necessary to attack the problem of medical economics. And truly this is more complex than any theorem ever conceived by Euclid or his disciples! Chapters on the general practice of medicine, specialists and group practice, health services, workman's compensation, analyses of the incomes of physicians and their public are clearly and succinctly discussed. He then summarizes the situation in Europe, with terse comparisons when necessary to point out differences in public customs and requirements.

In his chapters on "Medical Needs in the United States," "Some Suggested Methods of Improvement," and "Where do we go from Here?" Dr. Cabot critically analyzes our needs according to his own ideas. He freely criticizes the attitude of the American Medical Association in opposing all change except that emanating from Dearborn Street, but offers no panacea and backs no other single plan. However, he seems to align himself with "those practitioners under forty-five years" whom he states are all liberals and who are for changes in the existing order. As one who is really under that age, the Reviewer cannot subscribe to his appraisal. There are still a large number of young physicians who prefer the process of evolution to that of revolution and who only occasionally use the airplane as a means of transportation.

If Dr. Cabot can be said to offer any prophecy, it would be the future development of the group clinic in its several different forms. Perhaps that is because Dr. Cabot has usually been engaged in some form of group practice. On the whole the book is thoroughly readable and is recommended for physician or layman.

E. T., Jr.

NEW BOOKS.

Gynecological and Obstetrical Tuberculosis. By EDWIN M. JAMESON, B.S., M.D., Fellow of Trudeau Foundation; Attending Surgeon, Saranac Lake General and Reception Hospitals. Pp. 256; 31 illustrations. Philadelphia: Lea & Febiger, 1935. Price, \$3.50.

The Theory and Practice of Anaesthesia. By M. D. NOSWORTHY, M.A., M.D., B.CH. (CANTAB.), Anaesthetist to Westminster Hospital and Grosvenor Hospital for Women, etc. With a Foreword by I. W. MAGILL, M.B., B.CH. (BELFAST), Senior Anaesthetist to Westminster Hospital, etc. Pp. 223; 35 illustrations. London: Hutchinson & Co. Ltd., 1935. Price, 12/6.

Gastritis and Its Consequences. By KNUD FABER, M.D., LL.D.E., F.R.C.P.E. HON., Professor of Internal Medicine in the University of Copenhagen. Pp. 119; 48 illustrations. New York: Oxford University Press, 1935. Price, \$3.00.

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Roentgenbefund und pathologisch-anatomischer Befund bei Lungenkrankheiten. Versuch einer kritischen Vergleichung. 1. Teil: Text; 2. Teil: Atlas. By DR. MED. MAX VERSÉ, o. ö. Professor der allgemeinen Pathologie und pathologischen Anatomie; Direktor des pathologischen Instituts der Universität Marburg. Pp. 93 (Text); 144 illustrations (Atlas). Berlin: Otto Elsner Verlagsgesellschaft m.b.H., 1935. Price, Rm. 18.

Methods and Materials of Health Education. By JESSE FEIRING WILLIAMS, M.D., Teachers College, Columbia University, and FANNIE B. SHAW, M.A., University of Florida. Pp. 331; illustrated. New York: Thomas Nelson & Sons, 1935. Price, \$1.65.

Die Störungen des Lichtreflexes der Pupille bei denluetischen Erkrankungen des Zentralnervensystems. Beiträge zur Frühdiagnostik der Lues nervosa. By DR. MED. OTTO LÖWENSTEIN, seither ordentl Professor und Direktor des Pathopsychologischen Instituts der Universität Bonn, etc. Pp. 92; 31 illustrations: Basel: Benno Schwabe & Co., 1935. Price, Fr. 5.

A Bibliography of Two Oxford Physiologists, Richard Lower (1631-1691) and John Mayow (1643-1679). By JOHN F. FULTON, M.A. (OXON.), Sterling Professor of Physiology in the Yale University School of Medicine. Pp. 62; 7 illustrations. (Price not given.)

The Medicine-Man of the American Indian and His Cultural Background. By WILLIAM THOMAS CORLETT, M.D., L.R.C.P., (LOND.), Professor Emeritus of Dermatology-Syphilology, Western Reserve University; Fellow of the Royal Society of Medicine of Great Britain, etc. Pp. 369; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, \$5.00.

The Doctor and the Public. A Study of the Sociology, Economics, Ethics, and Philosophy of Medicine, Based on Medical History. By JAMES PETER WARBASSE, M.D. Pp. 572; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, \$5.00.

NEW EDITIONS.

Arthritis and Rheumatoid Conditions. Their Nature and Treatment. By RALPH PEMBERTON, M.S., M.D., F.A.C.P., Professor of Medicine in the Graduate School of Medicine, University of Pennsylvania; Physician to the Abington Memorial and Bryn Mawr Hospitals, etc. Pp. 455; 69 illustrations, 60 tables, and a colored plate. Second Edition, thoroughly revised. French translation of First Edition, 1933. Philadelphia: Lea & Febiger, 1935. Price, \$5.50.

A Synopsis of Regional Anatomy. By T. B. JOHNSTON, M.B., CH.B., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 460; 11 illustrations. Third Edition. Philadelphia: Lea & Febiger, 1935. Price, \$4.50.

The Principles and Practise of Medicine. Designed for the Use of Practitioners and Students of Medicine. Originally written by the late SIR WILLIAM OSLER, BT., M.D., F.R.S., Formerly Fellow of the Royal College of Physicians, London; Regius Professor of Medicine, Oxford, etc. Pp. 1196; 22 illustrations, 16 charts. Twelfth Edition; Revision by THOMAS MCCRAE, M.D., Fellow of the Royal College of Physicians, London; Professor of Medicine, Jefferson Medical College, Philadelphia, etc. New York: D. Appleton-Century Company, Inc., 1935. Price, \$8.50.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut.-Colonel, M. R. C., U. S. Army, etc. With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1573; 945 illustrations, including 283 portraits. Seventeenth Edition revised and enlarged. Philadelphia: W. B. Saunders Company, 1935. Price, Plain, \$7.00; Thumb Index, \$7.50.

PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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THE FEMALE URINARY ORGANS.

Ureteral Injuries. There can be no doubt that the ureter is injured in the performance of pelvic operations in a greater number of instances than the literature would indicate. If the operator realizes that he has injured a ureter he is naturally reticent about discussing it, while in many instances the injury is not recognized at the time that it occurs. In discussing this subject Brown¹ states that the diagnosis of ureteral injury can often be made during the operation, especially by careful inspection of the wound bed before peritonealization. In this manner he discovered such an injury in 7 of the 10 cases which he reports. Escape of urine from the vagina or the abdominal incision or complaint of incontinence following pelvic operations should always suggest the possibility of ureteral fistula, and should be investigated by cystoscopy when the patient's condition permits. Theoretically, this accident should be entirely preventable; in practice, however, it cannot be entirely eliminated. This is particularly true when there are congenital anomalies of the ureter, or when the ureter passes directly through tumor tissue. If the anatomy of the cervix and its neighboring structures is normal, the ureter lies 1.5 cm. from the uterus at the level of the internal os, and 1 cm. from the cervix at the vaginal reflection. These distances are increased when the bladder is dissected off the anterior wall and retracted downward and forward, while upward traction is made on the uterus. Therefore, if the dissection and retraction are properly done, and clamps or sutures are placed as close as possible to the uterus, the safety of the ureter can be guaranteed. In the presence of complicating conditions the most effective protection for the ureter lies in its exposure throughout its entire course through the parametrium. No attempt to remove the parametrial tissue should be made until this precaution has been observed. The introduction of

ureteral catheters preliminary to total hysterectomy may be of great value, although it is occasionally impossible to palpate the ureter even with the catheter *in situ*. Prevention of ureteral injury during vaginal hysterectomy depends first, upon the proper selection of cases, with elimination particularly of intraligamentous fibroids; second, upon making strong downward traction on the cervix while the bladder is dissected off the anterior wall of the uterus and by subsequent retraction of the bladder anteriorly; and third, by placing parametrial sutures as close as possible to the uterus. By observing these precautions he has not injured the ureter in a large number of vaginal hysterectomies. During the removal of intraligamentous cysts, the ureter may be safeguarded by blunt dissection of the tumor from its bed; in no case should adherent strands of tissue be cut until their nature has been determined. With fibroids developing within the cervix, danger may be avoided by splitting the uterus from the fundus downward and enucleating the tumor, after which the parametria may be clamped and cut as close as possible to the collapsed capsule.

A wide variety of procedures is available for the repair of an injured ureter and proper selection depends upon the type and location of the lesion, the time of discovery and the general condition of the patient. When complete section of the ureter is discovered before closing the abdomen, the most successful repair consists in implantation of the proximal end into the bladder. He has done this five times with primary healing in all. In high injuries, vesical implantation may be impossible and in such cases end-to-end anastomosis over a large catheter appears most promising but should always be accompanied by drainage of the kidney pelvis through a pyelostomy or ureterostomy above the line of repair. Should the condition of the patient be so alarming as to prohibit attempts to repair the injury, the proximal end may be doubled upon itself and ligated with a non-absorbable ligature, or it may be carried out through the incision or into the vagina, thus creating a fistula to be treated later.

Incomplete section of the ureter may be repaired by simply closing the defect, providing that no more than one-third of the wall is involved. If the damage is more extensive, the section should be completed and the proximal end implanted into the bladder. Bilateral ligation of the ureters should be treated by immediate laparotomy with removal of the ligatures if the patient's general condition will permit, otherwise bilateral pyelostomy must be performed with the hope that the ureters may be restored when operation can be tolerated. Postoperative ureterovaginal fistula should be treated expectantly for a time, since spontaneous healing occurs occasionally. If drainage continues for more than 6 weeks, one should attempt to conserve kidney function by transperitoneal implantation of the ureter into the bladder, which is generally preferable to nephrectomy.

In reporting 16 cases of accidental ureteral injury, Stevens² states that in 4 cases perforation occurred during cystoscopy, in 5 the ureter was injured during hysterectomy, in 2 during the removal of pelvic cysts, and the other cases during various pelvic operations. The left ureter was injured in 10 cases, the right in 5 cases and both ureters in 1 case. Ten patients recovered, 6 with good kidney function, 3 with probable destruction of the kidney and 1 after nephrectomy. Two

patients died. The 4 cases of perforation recovered, 1 following evacuation of a periureteral abscess, the others without complications. Regarding the treatment of such injuries he states that if a ureter has been completely severed or badly crushed, suture of the proximal segment into the distal or end-to-end anastomosis over a catheter has proven satisfactory. In the latter operation he also advises drainage of the kidney by inserting a ureteral catheter into the ureter through an incision above the anastomosis, and the kidney is drained temporarily through the loin by means of this catheter. Uretero-vesical anastomosis, preferably retroperitoneally, has given some good results, but must be done without tension on the suture line. If anastomosis is not feasible, infection is absent and the opposite kidney is healthy, ligation of the proximal end of the ureter is justifiable, but if the kidney is infected, nephrectomy is indicated when the patient has recovered from the shock of the primary operation. If the function of the opposite kidney is not satisfactory, nephrostomy, ureterostomy or intestinal implantation of the ureter are to be considered. If the ureters have been accidentally ligated and deligation is too hazardous, temporary drainage by means of nephrostomy is usually indicated until the ligature has been absorbed and drainage reestablished. Deligation is often attended by hemorrhage and is usually difficult, especially if attempted some days after operation.

From Rotterdam comes a report by ten Berge³ stating that he has implanted ureters into the bladder 4 times and has done an end-to-end anastomosis 3 times, and he found that after the latter operation the kidney function and pelvis remain normal for a longer period of time. In 3 of the 4 implantation cases hydronephrosis and pyelitis developed. The plan which he follows in uniting the cut ends of the ureter is as follows: the proximal portion of the ureter is incised longitudinally a short distance above the cut end and 2 tubular drains are inserted, 1 directed toward the kidney to drain the urine, the other directed toward the bladder. Over this latter drain both cut portions of the ureter are threaded and the ends are sutured together with 3 or 4 fine linen sutures. These drains are then led extraperitoneally to the abdominal wall in the region of the anterior, superior iliac spine. Since the site of the anastomosis is kept dry, there is very little danger of infiltration with later stricture formation. The drains are removed in from 2 to 3 weeks, and the incision in the ureter through which they passed closes itself in a few days.

After a urinary fistula has formed as a result of ureteral injury, if it does not close spontaneously, surgical repair will often be considered, as a patient who is constantly wet with urine is most miserable as well as a social outcast. However, surgical repair of such a fistula, as previously stated, may be quite a hazardous procedure. It is well to remember, as Sears⁴ points out, that modern Roentgen ray therapy can destroy normal and diseased kidneys. The intricate epithelial structure of the kidney is replaced by connective tissue. The vascular and glomerular units are the last to be affected. He reports a case of renal fistula which was cured by irradiation and he considers such therapy a safe procedure, provided the treatment is given by an expert roentgenologist.

Ureteral Calculus. When a stone becomes lodged in juxtavesical portion of the ureter the vaginal approach to this portion of the ureter has often been recommended. Kneise⁵ objects to the vaginal approach because of the frequent inability to find the stone at the time of operation even though it was palpable before. The relaxation of anesthesia permits the stone to slip up the ureter. In the operation which he advocates, after opening the abdomen through a midline incision, the uterus is pulled out of the wound, the bladder peritoneum is opened and the bladder is pushed well down from the uterus as in the Wertheim operation. The region of the entrance of the ureter into the bladder is slowly and carefully exposed so as not to injure the vessels in the broad ligament. The peritoneum is free laterally and the superior vesical artery is in the field and below it is the ureter. If the stone is palpable it is not necessary to free the ureter from its bed. If the ureter is very thin and presents a hydroureter above the stone, the urine is drawn from the ureter with a syringe so as to minimize peritoneal contamination. Before opening the ureter the patient is placed in the Trendelenburg posture and the surrounding field protected with gauze pads to prevent soiling with urine. While the assistant presses over the ureter proximal to the stone, a small incision is made over the stone and it is gently squeezed out or is extracted with forceps. The ureter is closed with a few fine sutures in the outer coats, the bladder peritoneum is sutured and the wound closed. In this technique it is not necessary to ligate the uterine vessels or sacrifice the adnexa of the affected side as usually described in textbooks. The method is only to be applied in cases where the stone is within 5 cm. of the ureteral orifice. Stones higher in the ureter should be approached by the lumbar extraperitoneal method.

Ureteral Obstruction in Cervical Cancer. When cancer of the cervix advances to the point that there is involvement of the broad ligament, it is only a question of time until the ureter becomes obstructed. In a study of this type of ureteral obstruction Drexler and Howes⁶ found that in every case the chief complaint is pain, ranging from a dull ache to a severe colic on the affected side. Usually the patient complains of a constant dull pain located deeply in the groin and referred to the thigh and leg, often simulating an attack of sciatica. It is frequently referred to one or both kidneys, especially when complete occlusion of the ureter has taken place with dilatation of the ureter above the obstruction. The patient often develops a marked distaste for food but with removal of the ureteral obstruction the appetite returns and the gain in weight is rapid, in some instances from 10 to 100 pounds. On physical examination through the rectum a moderate degree of induration, which is tender to touch, can be felt extending laterally. Cystoscopy with ureteral catheterization and pyelography establishes a positive diagnosis and in practically all cases the obstruction will be found in the terminal portion of the ureter. From their autopsy findings they believe that these strictures are the result of pressure on the ureter from invasion of the broad ligament by the malignant process itself and therefore they deem it necessary to direct therapy to this area with the same vigor as the primary lesion in the cervix has been attacked. Up to the present time no satisfactory radiation therapy has been devised for the broad ligament, although many methods have

been devised. Their most satisfactory results were obtained not from irradiation but from ureteral dilatation. The ureters were dilated about every 14 days with the instillation of 1% silver nitrate solution into the kidney pelvis. In many cases catheterization was at first difficult but filiform bougies were eventually passed by the point of obstruction. These were allowed to remain *in situ* for 48 hours and then followed by larger bougies or catheters. In the presence of infection, especially with marked elevation of temperature and a large amount of infected residual urine in the kidney pelvis, the catheters were allowed to remain *in situ* for several days. Occasionally nephrectomy was necessary. Although they have transplanted the ureters into the sigmoid in 2 cases, they feel that this procedure is too hazardous. Implantation of the ureters into the loin causes little shock and is technically much simpler to carry out and should be done where ureteral dilatation has failed.

Bladder Fistulas. In reporting 17 consecutive successful closures of bladder fistulas, Schmitz⁷ states that certain areas in the genital canal of any case are very important. All ulcerated areas in the bladder must be healed before any operative procedure is attempted, calcareous deposits should be removed as nearly as possible and bladder infection reduced to a minimum. Before operation the opening in the bladder must be accurately located by cystoscopy and its relation to the ureters and the patency of these structures must be ascertained. He advises against freshening the edges of the defect. In most textbooks dealing with fistulas, the suggestion is made that after the tract is freed the hard, firm edges of the opening should be carefully cut away. He warns against cutting anything away because all the tissue is needed in the repair and he considers it important to sacrifice nothing. The edges should be freed and turned in and the raw surfaces brought together as near the free margin as possible. By saving all tissue, if a failure should result, the opening will not be any larger than the original defect. It is important to make a free and wide dissection of all possible surrounding tissue. No suture will hold in soft tissue under tension and the only way to avoid tension is to mobilize structures. There must be sufficient bladder wall available not only to allow a closure of the opening but also to permit the placing of one or two rows of supporting sutures. To accomplish this requires a willingness to free tissues in all directions. The manner of placing sutures is important in two ways. A pucker should never be caused. If tissue buckles, surface adaptation is interfered with and the results are jeopardized. If working near the ureters one should place the sutures so that they follow the long axis of the tube and not across it. A non-absorbable suture should never be used in the bladder. If the catgut does not hold it is almost surely a fault in the operative technique and not the suture material which should carry the blame. Another important point in suturing these wounds is the obliteration of all dead spaces. One must suture the deeper to the more superficial structures, or pockets will develop which may undo the best operative procedure. After the fistula has been closed an iodoform pack is placed in the vagina along the suture line in order to prevent oozing and to aid in holding the raw surfaces to one another. It also reduces the bacterial flora to a minimum during the early postoperative period but should be removed at the end of 24 hours. A catheter is always introduced into the bladder at the end

of the operation and fixed there and allowed to remain for at least a week. Posture is very important in the after-care of these patients. One must try to drain away as much urine from the suture line as possible, not merely to keep the incision dry but to prevent even the slightest pressure upon the repaired area. If there is only a tiny bit of constant fluid pressure, seepage may occur. To obviate this, one should make the most dependent portion of the bladder that area farthest away from the suture line. In other words, in all posterior fistulas, and this means practically all of them, the patient should be placed flat on the abdomen with the head of the bed slightly elevated. This position must be maintained for at least 5 days, no matter how uncomfortable the patient may be. After this a little lying on the side and gradual turning to the back is allowed. The nursing care of these patients must be perfect. The drip of the catheter must be under constant observation so that no possible backing up of urine can occur as the result of blockage. The catheter itself is run down between the patient's legs and out at the foot of the bed, never over the side, so that the urine will fall gradually to the bottle by gravity and not be forced to flow over even a slight elevation. The tube is protected by sandbags so that the legs have no chance to compress the lumen, and it is irrigated once or twice daily with boric acid solution. While it may seem that we have gone into quite some detail in presenting the work of Schmitz, it is only by paying strict attention to such details that a satisfactory result may be expected in many of these cases, as those who have tried to repair extensive fistulas have found out for themselves.

At the Mayo Clinic, according to Stephenson and Masson,⁸ these cases are repaired by a modification of the method proposed by C. H. Mayo. After a thread is passed through the fistula at cystoscopic examination, a silver wire is drawn through the tract to act as a guide. The vagina is incised in a transverse direction on each side of a circular cut about the fistula and the base of the bladder is separated from the anterior vaginal wall. With the wire as a guide, dissection is carried well up toward the mucosa of the bladder and a purse-string suture of 00 chromic catgut is placed in the muscular layer. The greater part of the fistulous tract is excised and the vaginal end of the wire is grasped in a blunt hemostat. By making traction on the other end of the wire, the stub of the fistula is inverted into the bladder and the purse string is pulled tight. Reinforcing sutures of catgut are placed in the longitudinal axis and the transverse cut in the vaginal wall is closed separately, using interrupted sutures of silkworm gut. When the two lines of suture can be separated by normal tissue, the chances of permanent closure are good. A retention catheter is left in the bladder for about 10 days. In a few cases in which the vaginal approach is impracticable, either because of the position of the fistula or because the vaginal orifice is so small, it may be advisable to use a transvesical approach. The above description of the operation makes it seem so simple that one might expect uniformly satisfactory results, but such is far from the truth. Repair of the fistula is not effected at the first attempt as a rule, as was seen in the review of cases encountered at the Mayo Clinic. Of 24 cases with vesicovaginal fistulas, the condition of 17 was considered suitable for operation. There had already been

48 attempts at closure on these 17 women. While they were under care at the clinic it was necessary to do 23 operations; 4 of the cases are not entirely cured as yet and the end-result of treatment on 1 other is questionable. Usually if the fistula is 1 cm. or less in diameter, good results can be expected. However, the prognosis of any one attempt is not good if the field in which one is working is mainly scar tissue resulting from previous operations. Sometimes it is impossible to secure sufficient tissue with adequate blood supply to allow closure of the defect, and transplantation of the ureters into the sigmoid becomes necessary. It is probably wise to transplant the ureters in 2 stages, although in selected cases Coffey's second technique, in which both ureters are catheterized and transplanted at the same time is highly satisfactory. The closure of a small fistula by electrocoagulation has been suggested in recent years by European surgeons, but at the Mayo Clinic they have had no experience with the method. They feel, however, that best results with such a method will be secured when the fistula is not more than 1 or 2 mm. in diameter.

Non-purulent Urethritis. This condition, which is also known as granular urethritis and cystalgia, is discussed by Ormond,⁹ who states that it is a benign and very common ailment which is often overlooked. He believes that it is a urethrotrigonitis caused primarily by congestion and secondarily by infection. In this condition there are urinary symptoms but no abnormal urinary findings or else very minor ones. The condition is found at all ages after puberty, though most frequently in middle age. The most common symptoms are frequency of urination and dysuria, more marked during the day, while at times there is marked urgency. The treatment of the condition consists of dilatation of the urethra with graduated dilators and the instillation into the bladder of a mild antiseptic such as argyrol or mercurochrome once or twice a week. Occasionally it may be advisable to apply 10% silver nitrate solution to the upper urethra and bladder neck. The urine should be rendered bland and hot sitz baths or douches often give comfort. It should be remembered that recurrences are common, sometimes after many months.

Stricture of the Urethra. Although stricture of the male urethra is recognized as a common ailment, in the female urethra stricture has usually been considered an infrequent condition, and for this reason a careful examination for its presence is seldom made. In discussing this subject Wynne¹⁰ considers any obstruction to the passage of a sound that will pass the meatus as a clinical stricture, except a tumor, stone or other foreign body. Obstructions due to scar tissue, not involving the urethral walls, are not strictures although the symptoms are similar. The measurements made by various investigators show that the normal meatus measures from 18 to 30 F. and the majority is from 23 to 30 F. The finding of so many strictures at the meatus which have been reported by other observers suggests that they consider the "ring" type meatus as a stricture if it is of a caliber less than the average. Wynne is not convinced that a "ring" type meatus should be considered as a stricture even when small unless there is other evidence. It is a simple matter to excise a small wedge of the posterior portion of the meatus for microscopic sections and at the same time effect a cure if the size of the meatus is the cause of the symptoms. In 36 women

he has found an area of narrowing which was apparently abnormal and in those that occurred above the meatus the narrowing was of smaller diameter than the meatus. Gonorrheal urethritis was the most common known etiologic factor, although childbirth caused sufficient injury to the urethra in certain instances for stricture to develop. In nearly half of the series the etiology was not determined. As to location, 24 strictures occurred in the lower third of the urethra; 3 of these were at the meatus and 3 just within the meatus. There were 3 strictures of the middle third, 6 were in the upper third and 3 of these involved the sphincter. There was 1 generalized stricture beginning a few millimeters above the meatus. There were no multiple strictures in the series. The complaints of these patients were numerous, consisting most frequently of burning on urination and frequency and of less importance were complaints of nocturia, urgency, dysuria, hematuria and dribbling. Dilatation of the urethra with Hegar dilators was performed on the average from 4 to 8 times at intervals of from 1 week to 2 months. Thirteen women were observed from 1 to 8 years and were completely relieved when last seen, 8 were improved and 1 was unimproved. Temporary relief was obtained in 3 cases for from 4 months to 1 year, while the remaining cases in the series have not been followed sufficiently to report. Wynne does not believe that stricture of the female urethra is by any means a common ailment but it is a distinct entity which will usually respond to proper treatment.

Carcinoma of the Urethra. There have appeared in the literature reports of 149 authentic cases of carcinoma of the female urethra, but the case reported by Menville and Counseller¹¹ is apparently the first case of mucoid carcinoma of the female urethra which has ever been reported. An interesting feature of their case is the appearance of inflammatory tissue in the specimen removed for biopsy. Since carcinoma of the female urethra grows slowly and produces symptoms relatively late, it is practically impossible to detect a lesion in its early stages. The symptoms and signs are not typical even in the late stages of the disease, therefore the only reliable method of diagnosis is biopsy. Yet, in this case it has been shown that it is possible to arrive at an incorrect diagnosis even with biopsy. The dense infiltration of inflammatory tissue along the periphery of the urethral growth offers a satisfactory explanation for the inflammatory tissue in the specimen. It is interesting to note that the sensation produced by the urethral mass in this case was similar to that produced by a prolapsed uterus which had been present 38 years previously. Of significance is the fact that for 15 years difficulty in voiding was, with the exception of one attack of acute retention; and the presence of the mass between the labia, the only symptom referable to the urethral growth. It was also noted that an unusual type of urethral caruncle was present 14 years previous to its ultimate removal, while the absence of induration around the urethra was another interesting fact. It has been estimated that the average age at which carcinomas of the female urethra are seen is 53.4 years. The lesions are either in the external part of the urethra or involve all of it. Rarely are they in the posterior part of the urethra. These tumors are of slow growth and not infrequently the first symptom or sign noted is a metastatic nodule in the inguinal nodes. The most frequent symptoms and signs are difficulty in voiding or reten-

tion of urine, hematuria, tumor or metastasis, pain or dysuria, frequency and a discharge from the meatus. The most common finding is a non-pedunculated, indurated growth. In addition there may be tenderness, ulceration and a tendency to bleed. The lymphatic vessels of the female urethra drain into the external iliac, hypogastric and sacral nodes. Results of treatment, regardless of the method used, are highly unsatisfactory. Good results in some cases have been reported following surgical procedures, irradiation, or both. The best prognosis is offered in cases in which the lesion is localized in the anterior part of the urethra, where it can be totally removed by surgical measures.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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THE TREATMENT OF SYPHILIS BY INDUCED FEVER.

APPLICABILITY, CURRENT METHODS, RESULTS.

Introduction. The treatment of various stages of syphilis by induced fever has progressed rapidly with a series of important transitions during the past half decade. Mortality, the first consideration, has fallen rapidly with the establishment of a technique. A series of figures collected by Stokes and Pillsbury¹ for malarial therapy up to

1933 showed a range from zero to 32%, with an average of 12.7% deaths. Since the principal groups in this tabulation were collected, the rates of experienced American malarial therapists quoted as 0.5% (Cole),¹ 1% (O'Leary),¹ 2% (Osborne),¹ have fallen to even lower figures, such as O'Leary and Welsh's² last-quoted estimate of 0.57% in the final 200 cases, as compared with 5% in the first 100 treated. Jones and Spencer³ have reported a series of 47 cases with no deaths. On the other hand, a very recent report by Karnosh and Williams,⁴ in a series of 580 patients, returns the mortality practically to the average of previous years, namely, 12.7%. In the estimation of mortality from fever therapy procedures, a personal equation inevitably enters into interpretation, and the figures are markedly affected by the character of the material, which, of course, is much more favorable in youthful patients in the early stages of neurosyphilitic involvement than it is in late and degenerative material of public institutions. It is clear, however, that two things materially affect the mortality of fever therapeutic procedures. The first is the experience of the therapist, and the second is the development of special facilities for the work. The very great importance attached to these two desiderata is borne out in practically every society discussion of fever therapeutic problems. Since malaria remains the least controllable and the most beset by complications of any of the fever therapeutic methods, its mortality figures may be accepted as representative of the greatest rather than the least risk which the patient is asked to assume when his infection is treated by non-specific procedures. With the fall in mortality conditioned by greater experience of fever therapeutic methods, there has come a notable extension of the field of usefulness. Within the past several years, the procedure, at first confined to the treatment of parietic neurosyphilis, has been extended to asymptomatic neurosyphilis, to early syphilis with prophylactic intent, to prenatal syphilis, especially when complicated by interstitial keratitis and obstinate osseous lesions; to malignant precocious tertiarism in syphilis, to refractory osseous lesions in general, to serologic fastness and even to the treatment of the chancre (Kyrle).⁵ This enthusiasm, while understandable, is not always commendable. It should be clearly understood that the justification for employing a non-specific method in a stage of syphilis such as the primary lesion, in which specific methods of known high effectiveness already exist, is experimental, and experimental in the direction of increasing inaccessibility and difficulty rather than increasing simplification and availability. The emphasis on central facilities, individual experience, complicated technique and especially trained assistants alone, for the time being at least, raises insuperable objections to the attempt to popularize fever therapy for the general treatment of the earliest stages of syphilis.

The notable tendency toward simplification, together with the falling mortality of fever therapy procedures, will, however, in the future, probably render them increasingly available as adjunct treatment for refractory aspects of the disease in the above mentioned fields. Simplification is taking place primarily through the elimination of electrical agents for the induction of fever and by the increasing usefulness and safety of certain types of non-specific protein therapy, notably with the H fraction of typhoid antigen.

Classification of Methods. A very useful classification of current methods of fever therapy is provided by Tobias,⁶ which is quoted as follows:

1. Inoculation with infectious disease: (a) Malaria (tertian); (b) recurrent (relapsing) fever; (c) sodoku (rat-bite fever).

2. Injection of avirulent bacteria and their products: (a) Tuberculin; (b) typhoid vaccine and its fractions; (c) gonococcus vaccine; (d) dmelcos (*Bacillus ducrey*) vaccine; (e) saprophytic vaccine (neosaproviton B).

3. Injection of non-specific chemical and biologic products: (a) Sodium nucleinate; (b) milk; (c) peptone; (d) turpentine; (e) sulphur (sulphur in oil, or sulfosin); (f) blood (autohemotherapy).

4. Physical measures: (a) Hot baths; (b) diathermy (high-frequency); (c) short wave (radiotherapy or oscillotherapy); (d) infra-red radiation (hyperpyrexator); (e) hot air or conditioned air cabinets (hypertherm); (f) blankets and externally applied heat (hot-water bags, etc.).

Among these methods, relapsing fever, rat-bite fever, sodium nucleinate, turpentine and sulphur in oil can be rated as on the decline or definitely unsafe; at least so far as American practice is concerned, they may be regarded as retired, notwithstanding occasional favorable reports such as that of Beckman⁷ on sulphur.

Within the past 3 years there has been a notable development in the popularity and usefulness of typhoid inoculation, made possible first by the discovery of Nelson,⁸ that division of the total dose into two successive injections produces a much more delayed attainment of the always annoying immunity to the bacterial proteins. The fractionating of the typhoid organisms into the "M" and "H" portions, with the demonstration of satisfactory reactivity with minimum complications from the use of the H antigen has placed this technique of fever therapy on a much more satisfactory basis. The demonstration by Simpson⁹ and Epstein,¹⁰ that heated air alone in the first instance, and external applications of easily controlled heat by the hot (electric) blanket, could produce satisfactory temperature rises and gratifying therapeutic results, has been a long and important step toward simplification and safety.

None the less, even with the elimination of electrical current passing through the body, and the awkwardness and inconvenience of water baths and the comparative comfort for the patient produced by proper attention to his chlorid intake and output and control of his sweating, fever therapy has not yet become either a harmless or a simple procedure. The maintenance of the body temperature even of a comparatively healthy human being at high levels for a number of hours inevitably subjects the functional groups of body organs to stresses which are estimated with difficulty and which may at times lead to embarrassing or disastrous results.

Modus Operandi. The argument as to the relative importance of histiocytosis, phagocytosis and temperature rise as a spirocheticide and immunity reaction producer still continues, and has made little headway toward settlement as yet. Since Nonnenbruch's summary of the 16 possible modes of action of a non-specific or fever-producing agent in the treatment of disease (summarized by Stokes and Kulchar),¹

Neyman and Osborne¹¹ and Bierman and Fishberg¹² have made contributions to the physiologic reactions of the human body under pyretotherapy. The particularly extended study by the latter authors showed increases in the activity of the cooling mechanism, including rising skin surface temperature and increased sweat output, the surface temperature being lower than that in the interior of the body (short-wave radiation therapy). Increases as high as 400% in the velocity of blood flow were observed, and the average increase of pulse rate was 8.5 beats per minute for each degree of Fahrenheit temperature elevation. Systolic blood pressure usually shows a slight elevation followed by a gradual fall to a point below the original level. A free intake of fluid, when allowed, maintains the weight at approximately the pretreatment level and maintains the blood volume and blood viscosity. Apneic periods were observed in the respiratory rhythm, and the pH of the blood increases. Leukocytes show an initial fall of 25% to 30%, followed by a leukocytosis amounting to approximately 80% above the initial figure, with a great increase in the staff neutrophils and the appearance of immature forms indicating a stimulation of the bone marrow. The leukocytic response declines with repeated stimulation. A high sedimentation rate tends to fall as the temperature rises. Bierman and Fishberg,¹² as a result of their studies, emphasized the importance of the elimination of lactic acid through the sweat in the maintenance of the fever-treated body in acid-base equilibrium. Patients under fever therapy may reach an extreme degree of alkalosis, the pH of the blood reaching levels as high as 7.6. The enormous loss of chlorid through the sweat results in a chlorid-poor urine and a practically total cessation of the secretion of free hydrochloric acid in the stomach. A great increase in hemoglobin in response to the heightened oxygen demand of the patient in fever was observed. The authors mentioned very briefly and without emphasis the thermoethal effect of fever on bacteria; they point out that there is a reduction in the complement-fixing titer of the serum of individuals suffering with gonorrhea under fever therapy, and that similar reduction in the complement-fixing antibody of variously immunized rabbits has also been noticed. Neyman and Osborne¹¹ pointed out the slowness of the rise of temperature under externally applied heat, and state that the atmosphere surrounding the skin should not be allowed to rise in temperature above 130° F. unless the air is kept in constant motion by means of a blower or turbine. Blanket temperatures above 120° F. are regarded by them as dangerous. The deep body temperature is some 2 degrees higher than the subcutaneous temperatures of the thorax and abdomen. The authors believe that it should be possible to maintain the temperature of 42° C. for 1 hour, or 41° C. for two hours, within the body, which is necessary to destroy the *Spirochæta pallida*. In their discussion of the physiologic reactions to various therapeutic techniques, these authors state that cyanosis, the beginning failure of the respiratory apparatus, and a great tendency toward heat prostration is noticed in the more exhausting blanket treatment, as contrasted with the diathermic or radiothermic therapy.

Malarial Therapy. While malaria was originally introduced for the treatment of parenchymatous neurosyphilis, particularly paresis, there is a growing tendency to enlarge the scope of its usefulness. Freeman¹³

believes that those types of neurosyphilis which show minimal clinical signs in association with positive serologic reactions respond best to therapeutic malaria, and the author has seen the highest percentage of good results with asymptomatic neurosyphilis, paresis sine paresi, early dementia paralytica, early tabes and basilar meningitis. He is not enthusiastic for the results obtained in late tabes, advanced dementia paralytica, optic atrophy, nerve deafness, vascular occlusions and congenital neurosyphilis. O'Leary¹⁴ believes that asymptomatic neurosyphilis, which is to be anticipated in about one-fifth of all cases of the disease, and in which an adequate defense mechanism is apparently lacking against subsequent parenchymatous involvement, responds particularly favorably to the influence of malarial therapy, which is able to prevent parenchymatous neurosyphilis from developing in at least 50% of the patients. Ambler and Van Cleve¹⁵ are enthusiastic about the results obtained with malarial therapy in syphilitic interstitial keratitis. In the past 6 years the authors have treated 17 patients with inoculations of malaria with uniformly excellent results. Corneal opacities seem to be more completely and rapidly absorbed than with any other type of therapy, and no better results were obtained in patients who had had previous antisiphilitic treatment than in those who had had none. Recurrences were noted in 2 cases, occurring a few weeks after the inoculation of malaria, and responded well to the usual antisiphilitic treatment. In 5 patients, one eye only was involved when malarial treatment was begun, and the second eye did not become involved in any of them. There were no fatalities.

O'Leary and Welsh² report the experience of the senior author in the treatment of nearly 1000 patients with malaria over a period of 9 years. Stress is laid on certain disadvantages of treatment with malaria which have prevented the method from becoming used as a routine in cases of neurosyphilis. In 10% of the patients inoculated it was impossible to induce chills and fever, owing to an immunity to the infection. The therapeutic use of fever is contraindicated in the case of a debilitated syphilitic patient or in the presence of advanced disease in any of the vital viscera. While the original mortality rate was high, the authors now believe that death from treatment by malaria should occur rarely and only as the result of some accident. In the past 4 years of the authors' experience, the mortality rate has fallen to 0.57%. Occasionally a patient with dementia paralytica is made worse by treatment, in the authors' series the clinical symptoms being accentuated in 2.2% of the cases in which dementia paralytica, according to clinical evidence, was present. Of the 186 cases in which the clinical signs of advanced dementia paralytica were sufficient to warrant hospital care, a complete remission developed in 35%, and an additional 35% of patients were sufficiently benefited to be permitted to go to their homes. In 42% of the cases in which the spinal fluid was reexamined recently, the test was found to be reversed and completely negative in all respects. The authors expressed it as their observation that in more than three-fourths of the cases of asymptomatic dementia paralytica the clinical progress of the disease was arrested. Following treatment, the serologic tests of spinal fluid became reversed to complete negativity in almost half of the cases of asymptomatic neurosyphilis, in which routine measures had previously failed to have a favorable

influence on serologic characteristics. The results in the treatment of the tabetic forms of dementia paralytica and tabes dorsalis were likewise favorable in about half the cases, whereas among serologically negative tabetic patients with resistant complications, the crises and pains in the legs were only slightly benefited. Solomon¹⁶ has observed 174 patients following malarial therapy and confirms the figures of O'Leary in reporting that 65 (37.3%) were sufficiently improved to be able to resume work, while 22 (12.6%) were improved but not self-supporting. This means that about half of the patients were so improved that they were able to live in a normal community. Solomon believes that the amount of subsequent treatment and time play an important part in the serologic results. There is no complete parallelism between clinical and serologic results, and a negative reaction to tests of the spinal fluid is necessary before treatment can be discontinued. MacDowell¹⁷ believes that a gain in weight following malarial therapy has considerable prognostic significance, the more gradual the gain the more favorable and lasting the result. The author believes that the benefits derived from therapeutic malaria are of a practical nature, inasmuch as the patients who improve are able to engage in useful pursuits about the hospital even when not sufficiently recovered to be discharged and become self-supporting. Those who die, on the other hand, are spared a lingering death and gradual destruction of body and mind, and are usually in bed only a few weeks instead of months which was formerly the course which these cases pursued. Holzer,¹⁸ in 280 cases in which malarial treatment was advisable, found contraindications existing in 28%. These included trauma and operations on the skull, epilepsy, alcoholism, psychoses, heart disease, pulmonary, renal and other severe organic diseases. These figures indicate the need for critical selection before malarial treatment is instituted.

Foreign Proteins. The dangers and limitations attending the use of malaria have stimulated interest in the past few years in other means of producing hyperpyrexia. Typhoid vaccine has been recognized for some time as a safe and convenient method of inducing fever, as indicated by the work of O'Leary,¹⁹ Kemp and Stokes²⁰ and others, but the difficulty of producing a sufficiently high fever comparable to that of malaria has been a serious drawback to its more general adoption. This has been largely overcome, however, by the suggestion of Nelson,⁸ that a second injection of vaccine, given at the height of the fever produced by the first, is capable of inducing fever sufficiently high to be of therapeutic value. Recently Driver and Shaw²¹ have studied 19 patients with neurosyphilis and 2 with resistant syphilis associated with interstitial keratitis and iritis by the divided method of Nelson.

The technique advised by the authors is as follows: Fresh commercial typhoid vaccine was used, containing 1 billion organisms per cc. One cc. of the vaccine is added to 9 cc. of physiologic solution of sodium chlorid. One cc. of this mixture contains 100 million killed organisms. If a fresh vaccine is used, smaller doses are required. As a general rule, treatment is given on alternate days, although it can be given on successive days, providing the temperature has returned to normal, the reactions are well sustained and there are no other contraindications. Temperatures are taken rectally every half hour until the temperature

has risen to 104° F., and then every 15 minutes until it falls to 104° F. again. Thereafter the temperature is recorded hourly until normal. It is advisable to avoid the use of antipyretics for the relief of headache and other symptoms during the course of the treatment, as they may greatly diminish the fever reaction.

The first dose is given at any convenient time, preferably in the morning, followed by a second dose after the temperature has reached 100° F. or above. The interval between doses should not be less than 2 hours, and an interval of 3 to 6 hours is entirely satisfactory, providing the temperature has not dropped back to normal by that time. A course of treatment may consist of any number of reactions. As many as 10 to 16 have been given. Subsequent courses may be given to a patient with an equally satisfactory result after an interval of weeks or months. The initial dose of the vaccine rarely exceeds 10 to 15 million organisms. The authors believe that the method is an excellent substitute for malaria treatment and brings satisfactory fever therapy within the reach of a still larger group of patients suffering from neurosyphilis. Several courses of treatment can be given without the establishment of a permanent immunity and chemotherapy can be combined with it if desired. Higher temperatures made possible by this method clearly demonstrate the advantage obtained over the older method of inducing fever by the injection of typhoid vaccine.

Recently attention has been focused on the typhoid "H" antigen vaccine for debilitated patients who cannot stand the severe systemic reactions produced by whole typhoid vaccine. Schnitker²² has treated 25 patients with dementia paralytica physically unsuitable for treatment with malaria, full typhoid vaccine, or diathermy with typhoid "H" antigen (flagellar) alone and in combination with trypanasamid, and believes that the systematic serologic improvement obtained by this method compares favorably with the results secured with other forms of fever therapy. It has the following advantages: (a) Although the hyperpyrexia equals that obtained with full typhoid vaccine, the concomitant illness is far less severe. (b) It does not involve superimposing a second and perhaps lethal infection on an already existing one, as with malaria. (c) It does not involve the risk of burns and renal damage, as with diathermy. (d) The contraindications are but four, namely: (1) Severe cardiorenal disease; (2) active pulmonary disease; (3) severe cachexia; (4) acute infections with a rapid sedimentation rate.

Furthermore, the administration and control of this method of treatment is simple, and may be adopted by the general practitioner, both at the hospital and in the home. In the experience of the author, it has not been associated with complications or sequelae. The injections are given 3 times a week, intravenously, the initial dose used being 50 million organisms (killed bacilli equivalent). H antigen builds up a partial immunity as does whole vaccine, and increasing doses must be given at subsequent injections. The dose at the second injection is usually 200 million organisms, and after the third, 400 million, the number advancing 200 million per time up to the sixth injection (1 billion organisms). After this it is found better to increase the dose by 400 million organisms. Doses as high as 8 billion organisms have been

given. Patients who develop an immunity to the vaccine or who were initially immune because of antecedent typhoid were given paratyphoid A antigen H with good results.

Electrical and Other Physical Methods. During the past 6 years the increasing recognition of the fact that the common denominator of all methods was fever production, is largely, if not entirely, responsible for the striking clinical results which have been obtained by the use of the electrical methods of fever production. Neyman and Osborne,¹¹ King and Coeke,²³ Schamberg and Butterworth²⁴ and others have shown that diathermy in the treatment of paresis produces results comparable to that obtainable by malaria and other measures. Freeman, Fong and Rosenberg,²⁵ on the other hand, found diathermy much less effective than malaria. Among 50 patients treated with diathermy no remissions occurred, and while 10 patients improved, subsequent relapse was commonly observed. Since 1931, Simpson, Kislig and Sittler⁹ have been engaged in an investigation of the influence of an ultra-high-frequency field on neurosyphilis and other chronic infections. The essential difference between a 1-kw. radio transmitter and the apparatus used for therapeutic fever production is that the energy is concentrated between two large condenser plates instead of being directed from an aerial. The term "radiotherm" has been applied to this altered radio transmitter. The heating effect is produced by a vacuum tube oscillator, composed of two 500-watt radiotrons, producing a high-frequency field of approximately 10 million cycles per second (30-m. waves) between the condenser plates. The radiotherm differs from the diatherm used for fever production in that it operates at a frequency approximately 10 times as great. The spark gaps of diathermy produce damped waves, while the vacuum tube oscillator of radiothermy produces an even flow of continuous waves. In fever production by diathermy, alternating currents of high frequency pass between two large electrodes applied directly to the skin surfaces of the anterior chest wall, abdomen and back. If the electrodes are not maintained in direct contact with the skin surface, arcing occurs, resulting in skin burns.

In fever production by radiothermy the patient merely lies on a stretcher between the condenser plates; no electrodes are applied to the skin surface. However, short radio waves are concentrated in the drops of sweat which accumulate on the skin surface, occasionally producing arcing and burning, and consequently it became necessary to devise some means of allowing the patient to rest comfortably in an insulated air-conditioned cabinet ("Ketting hypertherm"). This has now been accomplished, and by passing a column of heated air over and under the patient it is possible to dissipate the sweat as it reaches the skin surface. Ordinarily it requires from 30 to 60 minutes to raise the rectal temperature from the normal level to the desired height (105° to 106° F.). Temperature, pulse and respiratory rate are recorded before the treatment is begun and every 10 to 20 minutes during the course of treatment, and a high degree of individualization is necessary because of the lack of uniformity in response to fever production by high-frequency methods. While formerly it was the custom of the authors to remove the patient from the cabinet as soon

as the desired temperature was obtained, subsequently maintaining the temperature by the use of heated blankets and flexible rubber electric pads, it is at present found advantageous to the patient's comfort to allow him to remain in the air-conditioned cabinet throughout the entire 5-hour febrile period. Simpson and his co-workers observe the following contraindications for the employment of sustained artificial fever: advanced age, myocardial or renal insufficiency, active tuberculosis, aortic aneurysm, or rapidly progressive late neurosyphilis. The sense of exhaustion commonly experienced by many patients can largely be overcome by supplying large quantities of chlorid-containing fluids both during and immediately after treatment, and the institution of the chlorid-replacement regimen has materially cut the time during which the patient has to remain in the hospital following the return of the temperature to the normal level. In 36 patients with some form of neurosyphilis the authors found that their results compared favorably with those obtained with other non-specific measures. While sufficient time or experience does not as yet permit a full evaluation of such treatment, the practical difficulties and the expense of the equipment involved, necessarily restricting its use to centers of investigation, it is probable that radiothermy represents a distinct advance in the pyretotherapy of neurosyphilis, and when reduced to a more available status may eliminate some of the more dangerous methods now in use.

In a more recent article by Simpson,²⁶ the results of treatment of 117 syphilitic patients are recorded. The course of treatment was completed on 87 of the group. The best results were obtained by combining specific therapy with at least 50 hours of sustained fever at approximately 106° F. Fever treatments were usually given weekly for 10 weeks, with 5 hours of sustained fever at each treatment. The antisiphilitic drug was injected $\frac{1}{2}$ hour before each fever treatment. After completion of the course, specific chemotherapy was employed at weekly intervals for 20 weeks. On 16 patients with dementia paralytica, 12 obtained complete clinical remission, 2 improved greatly, 2 showed moderate improvement and 1 demented patient was not improved. The spinal fluid reactions to the Wassermann and Kahn tests were reversed to negative in 6 cases. The blood serologic reactions were reversed to negative in 8. Among a group of 7 patients with taboparesis, subsidence of root pains occurred in all. Two experienced recurrence of the pain, but this was controlled by further treatment. In 4 of 5 patients with ataxia the gait improved, 1 being restored to a normal gait. In 9 patients with tabes dorsalis, root pains, in the form of crises or lancinating pains, were abolished in all. In 1 patient the symptoms of cord bladder were overcome. The spinal fluid reactions were reversed to negative in 2, became less positive in 3 and remained positive in 4, while the blood reactions to the Wassermann and Kahn tests were reversed to negative in 4 instances, became less positive in 3 and remained positive in 2.

Epstein and Cohen¹⁰ report a simple method of producing hyperpyrexia by carefully wrapping the patient in blankets and rubber sheeting. Oral temperatures of 104° to 105.8° F. may be produced and maintained for 6 hours by this means. The advantages are that it is cheap, there is no danger of electrical burns and it is less exhausting to the patient

than diathermy or the cabinet. Furthermore, it is easily transported, thus making it available to patients in private wards of general hospitals. Wilgus and Kuhns²⁷ also are enthusiastic for the use of the electric blanket. They report the results obtained among 500 patients treated with 5 different forms of fever therapy at the Elgin State Hospital and the State of Illinois Psychopathic Institute as follows: Typhoid vaccine: improved, 52%; unimproved, 28%; worse, 20%. Sulphur in oil: improved, 58%; unimproved, 21%; worse, 21%. Malaria: improved, 66%; unimproved, 20%; worse, 14%. Diathermy: improved, 72%; unimproved, 11%; worse, 17%. Electric blanket: improved, 78%; unimproved, 15%; worse, 7%.

Wagner-Jauregg,²⁸ the father of malarial therapy, cautions against accepting various electrical methods for fever production with too much enthusiasm, inasmuch as so little is at present known regarding the permanency of remissions obtained by these measures. He is, indeed, inclined to doubt whether they will be permanent, because treatment with the radiotherm in his experience had little effect on spinal fluid reactions. He believes that treatment with radiotherm may prove particularly valuable in the treatment of late tabes with positive spinal fluid and may prevent the development of general paralysis. The method does have some advantages over malaria, however, in his opinion, namely, the absence of danger of the transmission of other diseases and the shorter interval of hospitalization involved. Furthermore, the height of the temperature can be controlled and treatment can be distributed over a longer period of time than is possible with malaria. The costly apparatus, however, and a trained personnel do not at present make the method as practical as malarial therapy.

It is apparent from the above summary of recent literature that induced fever has unquestionably established itself as a valuable and, indeed, at times, indispensable aid in the treatment of certain phases of syphilis. While the choice of method is still unsettled and each seems to possess certain disadvantages to counterbalance its merits, continued research in this field will undoubtedly give us a safe, practical and relatively inexpensive method of producing hyperpyrexia.

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(Titles have been omitted for sake of brevity.)

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ORIGINAL ARTICLES.

INFLAMMATION AND BACTERIAL INVASIVENESS.*†

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I PROPOSE to discuss some observations gathered during the past few years concerning the relationship of inflammation to immunity.

Inflammation, broadly defined, is the complex vascular, lymphatic, and general tissue response to the presence of an irritant. The development of the inflammatory reaction consists of a series of dynamic and sequential changes which tend to localize and ultimately dispose of this irritant. It is with a study of some of these changes that we have been engaged.

Several years ago it was found that when a vital dye, trypan blue, is injected directly into the subcutaneous tissues of a rabbit, the dye rapidly diffuses into the tributary lymphatics, so that if these regional vessels are cannulated, the lymph is stained intensely with the dye. If, on the other hand, the same dye is injected into a prepared area of inflammation induced by a chemical irritant such as aleuronat, the dye fails to penetrate to either the draining lymphatic vessels or the regional lymph node.¹ The dye has evidently been *fixed* in the inflamed area. Furthermore it was observed that there is an important time relationship in this connection. The dye was found fixed as early as 30 minutes after the subcutaneous injection of aleuronat as an irritant. I shall refer to this fact later on, and to the importance of this early retention of foreign substances at the site of an acute inflammation. Subsequent experiments showed that the intravenous injection of this dye is followed

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by a rapid accumulation of trypan blue in the inflamed focus. Studies revealed that this accumulation is in part due to the increased capillary permeability in inflammation, and also, as just pointed out, to the inability of the dye to drain outward into the regional lymphatics.

The extent of increased plasma filtration due to capillary injury and increased capillary pressure at a point of injury is open to quantitative measurements.² By means of a vital dye, it was shown that with certain inflammatory irritants the normal permeability of capillaries is increased about twofold.* Particulate matter which is unable to pass through the normal capillary endothelium readily passes through the lining of such channels in an inflamed area.³ The increased permeability of capillaries in inflammation is an initial reaction. It has been detected as early as 2 minutes after the injection of certain irritants.

These findings are applicable to microorganisms. When bacteria such as *B. prodigiosus* or *B. pyocyaneus*, are injected into the circulating blood stream, they localize and are recovered from foci of inflammation in greater numbers than from surrounding normal tissues. This was found by culturing inflamed skin areas and by comparing the number of colonies obtained with those recovered from corresponding normal cutaneous regions. Bacteria when injected directly into an area of injury are likewise fixed *in situ* precisely as in the case of the vital dye described previously, and these microorganisms fail to disseminate to the tributary lymphatics as readily as they do under normal circumstances. The frequent localization of bacteria from the blood stream in a *locus minoris resistentiæ*, after preliminary trauma or other injury to tissue, is well known to pathologists and clinicians. Osteomyelitic conditions are the frequent consequences of such preliminary injury. My observations on the accumulation of bacteria in an inflamed area from the circulating blood stream may explain the mechanism of this phenomenon in terms of increased capillary permeability with subsequent accumulation and fixation of bacteria at the point of injury.³

Since antibodies are regarded as being closely associated with globulins, the demonstration of an increased concentration and of a retention in inflamed tissue of foreign proteins from the blood stream would obviously be significant in connection with the rôle of antibodies in specific infectious processes. A series of experiments revealed that horse serum injected into the circulation accumulates at the site of an acute inflammation from which it fails to

* The term "permeability" as employed in this discussion and in previous communications refers to the degree of filtration through the capillary wall. It is, however, understood that the increased filtration in acute inflammation involves as one of its most important factors an injury to the endothelial wall with increased permeability of the membrane as indicated by the passage of particulate matter.

drain away readily.⁴ The fixation of this foreign protein was found to be distinctly more pronounced in inflamed cutaneous tissue than in a corresponding irritated peritoneal cavity. These observations formed the basis for an explanation of the local anaphylactic phenomenon described several years ago in the ear of the rabbit by Auer.^{4,5}

Shwartzman described the reaction that occurs when a filtrate of *B. typhosus* is injected into the skin of a rabbit. Twenty-four hours later when the same filtrate or a filtrate of a non-related organism, such as the meningococcus, is introduced into the circulating blood, hemorrhagic necrosis frequently appears at the site of the cutaneous injection.⁶ In 1931, on the basis of the aforementioned studies on the accumulation and fixation of foreign proteins at the site of inflammation, I suggested that the intense cutaneous reaction following the intravenous injection of a bacterial filtrate may be the result of an accumulation of this substance in an area of skin already inflamed.⁷ The reaction does not necessarily have to take place with all bacterial filtrates or with all types of inflammatory irritants. The degree of permeability of the capillaries and the optimum synergistic action of two irritating substances on one another may modify the final manifestation. That the bacterial filtrate or other reacting material which is injected intravenously in order to induce the local skin reaction, may be chemically altered while in the circulation is perfectly possible. However this in no way modifies my original suggestion that the Shwartzman phenomenon may be conceived of as a non-specific reaction resulting from the accumulation in an inflamed area of an irritating substance. Siekles demonstrated that, following the cutaneous injection of a bacterial filtrate, intravenous injection of agar produces the typical hemorrhagic manifestation described by Shwartzman.⁸ This observation is in accord with the view that the phenomenon is a non-specific reaction. The histological studies of Karsner and Moritz,⁹ and the more recent work of Freund¹⁰ on the guinea pig, where silver nitrate was employed as the preparatory factor, have essentially confirmed by original viewpoint.* It is interesting to note in this connection that, although Shwartzman himself believes that the explanation here offered is untenable, this investigator has as yet produced but meager evidence to disprove this hypothesis. By diluting the skin preparatory factor, Shwartzman notes no detectable inflammatory reaction by gross examination prior to the intravenous injection of the filtrate. And yet a striking hemorrhagic and necrotic lesion is often elicited several hours after the intravenous injection of the bacterial filtrate.¹¹ The absence of gross evidence of inflammation at the prepared skin site does not neces-

* It is to be noted that with the exception of Freund's work with silver nitrate in which he obtained the Shwartzman reaction in about half of his guinea pigs, the skin preparatory factor has in all cases been a bacterial filtrate.¹¹

sarily indicate that the capillary wall is normal. As previously pointed out,¹² the increase in the permeability of capillaries in inflammation may occur extremely early and may in many instances produce little, if any, change that is detectable by gross or even microscopic examination. An increase in the functional filtration through the capillary endothelium, as indicated not necessarily by morphological evidence, but rather by the ability of foreign materials from the blood stream to accumulate in the prepared area, would adequately explain the Shwartzman phenomenon as a type of inflammatory reaction induced by the superimposition of an irritant concentrating from the circulating blood in a previously inflamed area.

The studies on accumulation and fixation of foreign proteins in inflamed tissue suggest perhaps a possible explanation for the phenomenon of the focal reaction in tuberculosis. When tuberculin is introduced into the blood stream of an animal with a tuberculous lesion, an intense inflammatory reaction may develop in the lesion. The mechanism of this focal reaction in tuberculosis is not understood. It is conceivable, in view of the experiments with horse serum, that in a like manner, tuberculoprotein may accumulate from the blood stream in the inflamed tuberculous lesion and, by its presence there, induce a local inflammatory reaction.

As was pointed out 3 years ago, these studies on proteins suggest the important rôle which circulating antibodies may play in the early stages of specific inflammatory reactions. For by their accumulation and fixation in such foci they doubtless play a significant part in reinforcing cellular factors which ultimately dispose of the irritant.¹³ The earlier studies of Opie on the Arthus phenomenon demonstrated clearly the protective action resulting from the fixation of the antigen at the site of the anaphylactic inflammation.¹⁴ In this connection the recent interesting work of Rich and McKee¹⁵ is noteworthy. These investigators showed that following the cutaneous reinoculation of pneumococcus Type I in animals immunized to that organism, an agglutinative response occurred in the tissue. It remains to be seen whether the agglutinative elements described by these workers are not in part the result of a concentration in the skin of antibodies from the circulating blood stream, owing to an increased capillary permeability following bacterial inoculation.

The mechanism of *fixation* whereby foreign substances or bacteria fail to disseminate readily from an acutely inflamed focus is referred primarily to an obstructive barrier in the form of thrombosed lymphatics and coagulated plasma in tissues distended with edema.¹⁶ Time does not permit description of the various experiments to substantiate this concept. The important evidences in this connection will be mentioned briefly.

In the first place phagocytosis does not play a significant rôle

in the reaction of fixation. This phenomenon occurs so early after the introduction of an irritant that there are still relatively few leukocytes present at the time. Furthermore microscopic studies at this period fail to reveal any trace of the phagocytosed material tested. Yet these foreign substances are prevented from reaching the regional lymph nodes.

Microscopic examination of such acutely inflamed areas reveals a tissue distended with coagulated plasma. The presence of a fibrinous meshwork forms a conspicuous feature of the injured part. Careful observation of small vessels invariably brings to view many of the lymphatics either completely or largely occluded by thrombi consisting of a delicate fibrinous reticulum. In the later stages of the reaction, many leukocytes are found embedded in its meshes.

Subsequent experimental evidences substantiated this concept of mechanical obstruction to account for the inability of foreign substances or bacteria to disseminate from an inflamed focus. For instance, it was reasoned that if this were the case, a testing substance, such as a dye or bacteria, would, when injected at the periphery of an inflamed area, fail to enter it. This was found to be the case.^{3,16}

The concept of mechanical obstruction was further established by a chemical test. Concentrated urea *in vitro* prevents the coagulation of blood, owing to its protein solvent action on fibrin. Preformed fibrin also tends to go into solution fairly readily in the presence of a sufficiently concentrated solution of urea crystals. When this substance is injected into a rabbit simultaneously with an inflammatory irritant, the reaction of fixation is inhibited. In such experiments the lymphatics are found unoccluded by thrombi, thus adequately accounting for the free drainage of substances from the inflamed area.¹³

The foregoing observations have offered a means of studying the mechanism to account for the differences in the invasive ability of various pyogenic organisms.^{12,17}

The intensity and rapidity with which an inflammatory irritant is circumscribed in a tissue area varies with the type of irritant. The speed with which an irritant causes a region to be walled-off by mechanical obstruction in the form of thrombosed lymphatics or a fibrinous network or both is necessarily an important index in determining its ability to disseminate ultimately into the circulating blood. This holds true if the irritant *per se* can readily drain through lymphatic vessels from the site of inoculation. That bacteria disseminate from the site of inoculation through lymphatics has been frequently demonstrated. It follows from this that if bacteria are employed as inflammatory irritants some information may be obtained concerning the invasive capacities of different microorganisms. This would depend on the type of inflammatory reaction which a given microorganism induces in the host. Pathologists

and surgeons are familiar enough with the localizing tendency of staphylococcus in contrast to the invasive property of the streptococcus. Can the behavior of various pyogenic organisms in tissues be related at least in part to their respective abilities of creating an early inflammatory reaction at the site of their inoculation which would tend to prevent, by the mechanism previously described, their dissemination to the tributary lymphatic nodes? It has been pointed out in a former communication that when a vital dye is introduced into an area at various intervals of time after bacterial inoculation of this site, the degree of walling-off of the infected focus may be determined by the extent to which the dye can drain into the regional lymphatics or, for that matter, ultimately into the blood stream. This method can perhaps be used as a clinical test to determine the patency of lymphatics, or, in other words, the degree of walling-off of an area of inflammation such as a pyogenic abscess or an inflammatory reaction in a cavity, whether the peritoneal, pleural, or joint cavity.

The observations presently to be described represent a comparison of three pyogenic cocci: *S. aureus*, *Strep. hemolyticus*, and Type I pneumococcus with regard to the rapidity of retention of trypan blue at inflammatory foci induced by these respective organisms.¹² The significance of such data in regard to an understanding of the invasive properties of these microorganisms will be pointed out.

When trypan blue is injected into the skin of a rabbit immediately after the inoculation of *Staph. aureus*, the dye readily diffuses to the regional lymphatics. If, however, an interval of only 1 hour elapses between the injection of the bacterial irritant and that of the dye, the latter fails to drain into the lymphatics. An area of inflammation induced by the staphylococcus organism becomes evidently very rapidly circumscribed. Microscopic studies fully substantiate this fact for lymphatic lumina are found occluded by fibrinous thrombi. In many areas, the injured tissues are distended by coagulated plasma.

In the case of Type I pneumococcus, the dye continues to reach the lymphatic nodes until a somewhat later stage, *i. e.*, about 6 hours after the inoculation of the microorganisms. Here again this observation is correlated by the finding of occluding thrombi in lymphatics. It is of interest to note the absence of fibrin in the extracapillary spaces of the skin of these infected rabbits.

The prompt walling-off response on the part of staphylococcus is contrasted with the delayed reaction of fixation in the case of the hemolytic streptococcus. When these organisms are inoculated into the cutaneous tissues of rabbits, trypan blue freely drains from the site of bacterial inoculation to the regional lymphatic vessels for almost 2 days. Throughout this period the lymphatics are patent, as evidenced both by their normal functioning and by

the distended and almost unoccluded state of their lumina. About 45 to 50 hours after the initial inoculation of the streptococcus, microscopic examination reveals plugging of lymphatics by dense leukocytic thrombi. At this time the area of inflammation is effectively circumscribed, for trypan blue injected into such an area is fixed and is unable to drain to the regional lymphatic nodes. These observations, recently confirmed by Dennis and Berberian,¹⁹ present an interesting paradox. Staphylococci produce in general little systemic effect owing to their intense local injurious reaction which fixes them *in situ*. Streptococci produce profound generalized effects on the organism as a whole because of their comparatively mild local reaction which allows them a relatively free penetration to the essential organs.

It is improbable that the interesting observations of Tillett and Garner on the fibrinolytic activity of hemolytic streptococci can offer an adequate explanation for this delayed fixation of trypan blue.¹⁸ Their own findings definitely show that this lytic effect fails to take place with the plasma clot of the rabbit which was the animal used in our studies. It is noteworthy that Dennis and Berberian have attributed the delay of the inflammatory fixation in the presence of streptococci to the production of fibrinolytic substances.¹⁹ Further studies, however, have caused these investigators to abandon this explanation.²⁰

It is more likely that in the case of human streptococcal infection the dissolution of fibrin acts as a synergistic agent to a more fundamental factor which holds true for both human and rodent types of infection.

Studies now in progress support this point of view. The Berkeley filtrates of several-days-old broth cultures of *S. aureus* induce an acute inflammatory reaction in the skin of rabbits which promptly causes retention of trypan blue (Table 1, Fig. 1).^{*} The reaction is essentially indistinguishable from that obtained when the microorganisms alone are injected. Heating the filtrate to 58° C for about 1 hour destroys the principle responsible for the reaction (Table 2, Fig. 2). The filtrate of a day-old culture is ineffective, whereas the day old culture of the organisms produces perfect walling-off of the inflamed area. This indicates that the *S. aureus* owes its necrotizing activity (which doubtless is an important factor in its ultimate localization) not merely to its presence *per se*, but in addition also to its ability to release a powerful exotoxin-like product. This soluble toxic, thermolabile material is capable of inducing sufficient capillary and lymphatic damage to produce a shunting off, so to speak, of the inflamed area.

* The technique used in these experiments has been adequately described previously.¹² In brief 2.5 cc. of 1% trypan blue in saline is injected in the foreleg of a rabbit in a previously inflamed area induced in the above experiments by bacterial filtrates. About 2 hours later the regional lymphatics are examined for the presence of the dye.¹

TABLE 1.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY FILTRATE OF STAPHYLOCOCCUS CULTURE.

Rabbit No.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
			Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
	Hrs. Mins.	Hrs. Mins.				
8-35	1.05	3.50	0	0	+	+
8-34	1.36	4.48	0	0	+	+
8-22	1.40	4.25	0	0	+	+
8-83	2.35	5.12	0	0	++	++
8-31	19.42	22.02	0	0	+	+
8-85	19.44	22.24	0	0	++	+++
98	20.20	22.50	0	0	Faint trace	+
9-74	22.28	24.39	+ to ++	+	+	++++
10-12	22.55	24.05	0	0	Trace to +	Trace to +

TABLE 2.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY HEAT-INACTIVATED FILTRATE OF STAPHYLOCOCCUS CULTURE.

Experiment No.	Type of staphylococcus filtrate.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
				Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
		Hrs. Mins.	Hrs. Mins.				
1	Inactivated Normal	17.50	20.55	+++	++	++	+++
		17.45	21.00	+	+	++++	+++
2	Inactivated Normal	18.05	20.20	++	++	++	+
		17.55	20.20	Trace	0	+	++
3	Inactivated Normal	20.10	22.25	++	+	++	+
		20.00	22.20	Faint trace	0	+	+
4	Inactivated Normal	20.40	23.10	++	++	++	+
		20.33	23.05	Trace	(?) Faint trace	+	+
5	Inactivated Normal	25.25	27.10	+++	++	+++	++
		25.43	27.35	+	+	++	+++

There is some evidence that this material resembles in many respects staphylococcus leukocidin.

In the earlier studies of Denys and Van de Velde²¹ these investigators pointed out that the action of staphylococcus leukocidin is not restricted solely to leukocytes, but that this material is injurious likewise to eosinophils, hematoblasts, red cells, and cells of

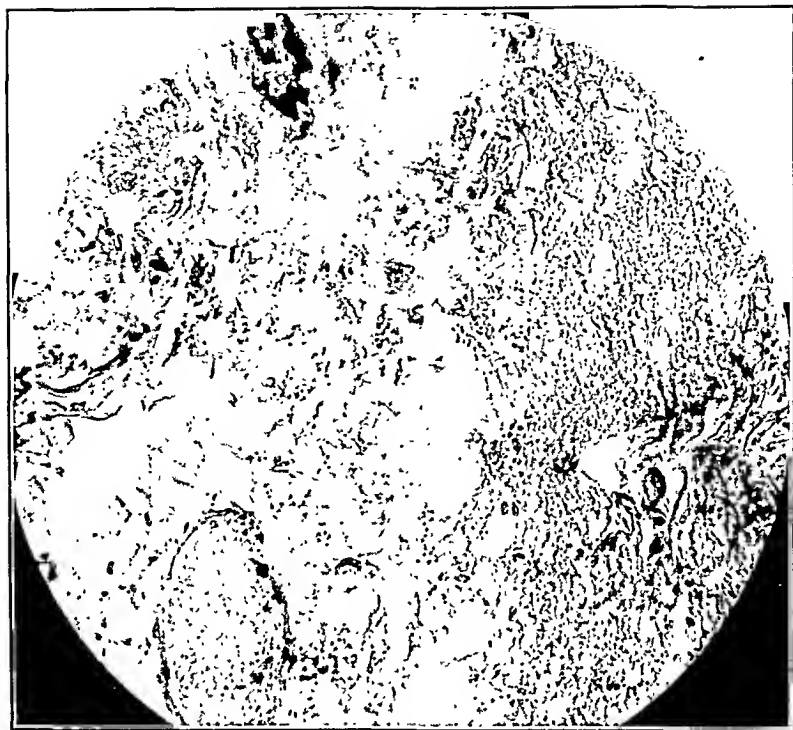


FIG. 1.—An inflamed area induced by the intracutaneous inoculation of about 1.5 cc. of the Berkefeld filtrate of a several-day-old culture of *S. aureus* (See Rabbit 8-85, Table 1). The inflamed area is of over 22 hours' duration. Trypan blue injected into this area failed to reach the tributary lymphatics. Note both the fibrinous thrombus occluding the lymphatic lumen, and the coagulated plasma in the tissue spaces.

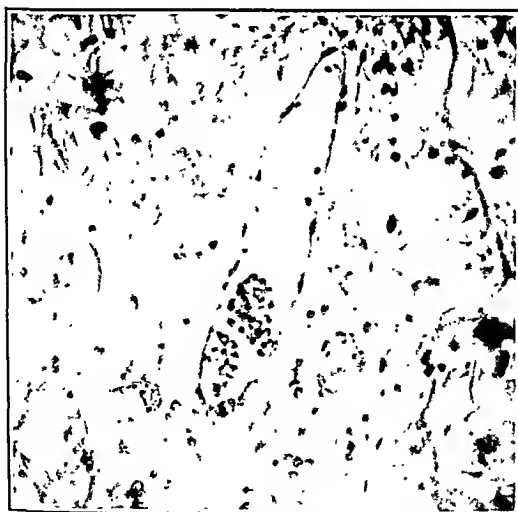


FIG. 2.—A lymphatic lumen in an area of inflammation induced by the inoculation of inactivated *S. aureus* filtrate. (This was accomplished by heating the filtrate at 58° C. for about 1 hour; see Exp. 5, Table 2.) The inflammation was of more than 27 hours' duration. The lumen is unoccluded. Trypan blue drained readily from this area to the tributary lymphatics.

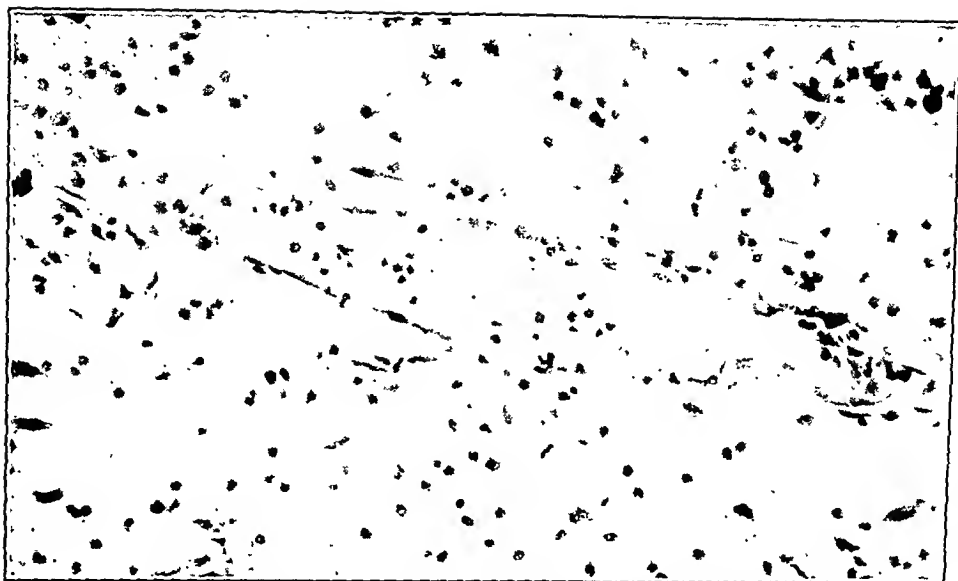


FIG. 3.—A lymphatic lumen in an area of inflammation induced by a Berkefeld filtrate of pneumococcus Type I. The inflammation is of more than 23 hours' duration (see Rabbit 8-77, Table 3). Note the unoccluded lumen in an area of edematous tissue with moderate cellular infiltration. Trypan blue readily diffused from such an area to the regional lymphatics.

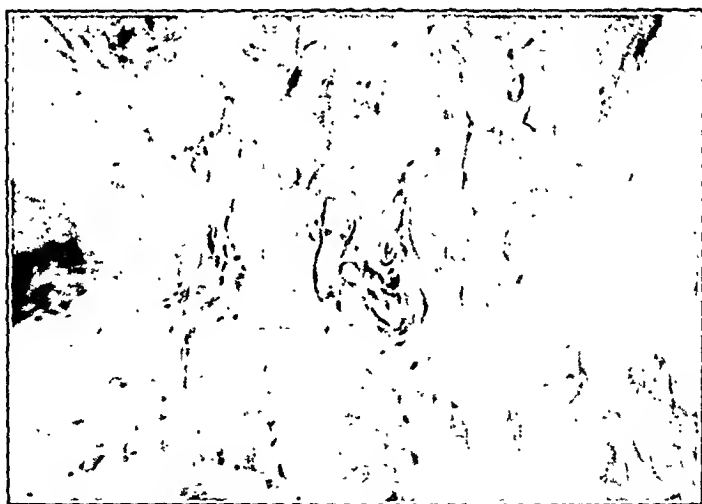


FIG. 4.—An inflamed area induced by the Berkefeld filtrate of a culture of hemolytic streptococci. The inflammation is of more than 52 hours' duration (see Rabbit X, Table 4). Note presence of unoccluded lymphatic lumina in tissue distended with edema. Typan blue diffused readily from this area to the regional lymphatics.

the sympathetic ganglia. Parker²² in 1924 described the production of an exotoxin by certain strains of *S. aureus*. The Berkefeld filtrate of her strains revealed a selective poisonous necrotoxic action for the skin of rabbits. The toxin was found to be thermolabile, being completely destroyed when heated to 55° for 1 hour. She recognized the resemblance of this material to leukocidin, but in a later study concluded that the necrotoxic action of the filtrate appears to be due to a different constituent from either the hemotoxic or the leukocidic one.²³ Burnet, on the other hand, is of the opinion that the various manifestations of staphylococcus exotoxin are due to a single antigenic substance. The leukocidin of *Staph. aureus*, according to this investigator, is identical with Parker's skin toxin.²⁴

Dr. Weld (née Parker) kindly supplied me with samples of her necrotoxic staphylococcus filtrate. This material injected into the skin of rabbits causes a pronounced edematous reaction. Dye introduced into such an inflamed area is fixed *in situ* and fails to diffuse to the tributary lymphatics. This same material heated for 1 hour at about 58° C. is rendered completely innocuous; *i. e.*, as far as the fixation of a vital dye is concerned.

Berkefeld filtrates of staphylococci which induce prompt cutaneous "walling-off" were tested *in vitro* on tissue cultures of guinea pig mesenteric lymph nodes. Direct examination and microscopic sections of the explants several days later showed relatively few normal cells toward the center of the tissue. There was hardly any migration of cells, and these had for the most part pycnotic and shrunken nuclei. Some cells showed nuclei disintegrated into intensely stained granular material scattered throughout the cytoplasm. The heated or inactivated staphylococcus filtrate, on the other hand, revealed no such injurious effects on the cells of explants. The leukocytes, primarily mononuclear phagocytes, showed normal migration at the periphery of the explants. These cells appeared perfectly normal in regard to their staining property and morphology.

S. aureus filtrate in contact with granular leukocytes obtained from an exudate caused these cells to become swollen and vacuolated. Supravital smears revealed these leukocytes as rounded, immobile cells with little staining of the granules. Evidence was also obtained that the total leukocyte count is lowered when this bacterial filtrate is maintained for some time in contact with an inflammatory exudate. Similar results were obtained by subjecting cells from the lymph of rabbits to unheated and heated filtrates of *S. aureus*. In conclusion these observations strongly suggest that the active principle in the filtrate of *S. aureus* which causes early lymphatic blockage is somewhat similar to, if not identical with leukocidin.

A number of authors including Much,²⁵ Gratia,²⁶ and Gengou,²⁷ have shown that *S. aureus* and its exotoxin are capable of causing

oxalated blood to clot. This, according to Gratia, is due to a thermostable substance which he calls *staphylocoagulase*.²⁶ Recent studies in collaboration with Mr. H. Walston have demonstrated that evidently "staphylocoagulase" plays no significant rôle in inducing the prompt fixation of trypan blue in the skin of rabbits treated with *S. aureus*. By treating the filtrate of this organism with glacial acetic acid, *staphylocoagulase* can be separated from the principle that induces fixation. The isolated "staphylocoagulase" produces clotting of citrated plasma in the test tube up to a dilution of 1 in 320 of the resuspended precipitate. And yet this material, when injected intracutaneously, although it is absorbed from the skin by lymphatics as indicated by the mild inflammatory cellular reaction in the regional lymph nodes, fails to exert a sufficiently powerful local reaction to obstruct lymphatic drainage by the formation of a fibrinous barrier. Trypan blue diffuses readily from the site of its cutaneous inoculation and the tributary lymphatics are found unoccluded. This indicates that "staphylocoagulase" evidently plays no rôle in inducing mechanical obstruction to lymph flow.* The latter is primarily referable to the powerfully necrotizing action *per se* of the staphylococcus microorganism and of its soluble toxin.

The filtrates of hemolytic streptococci and of Type I pneumococcus are utterly unable to induce any localizing response. The dye penetrates from such inflamed areas to the regional lymphatics even as late as 50 hours following the inoculation of streptococcal filtrates (Tables 3 and 4, Figs. 3 and 4). The filtrates of these latter microorganisms are evidently entirely innocuous.

TABLE 3.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY FILTRATE OF PNEUMOCOCCUS TYPE I.

Rabbit No.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
			Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
	Hrs. Mins.	Hrs. Mins.				
8-77	18.55	23.25	+	+	+	+
8-72	19.04	21.17	Trace	+	0	Faint trace
9-71	23.50	25.45	+	+	+	+
9-86	23.52	25.58	++	++	++	++
8-78	24.00	26.50	++	++	+	++
9-72	24.16	26.16	++	+	+	++
8-80	27.30	29.50	+	++	++	+

* Additional evidence corroborating this conclusion was obtained from the filtrate of a strain of *S. aureus* which failed to elicit the clotting reaction *in vitro* (*i. e.*, staphylocoagulase was evidently absent); and yet, when introduced into the tissues of a rabbit, the filtrate produced an inflammatory reaction with perfectly good fixation of trypan blue.

TABLE 4.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY FILTRATE OF STREPTOCOCCUS HEMOLYTICUS.

Rabbit No.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
			Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
	<i>Hrs. Mins.</i>	<i>Hrs. Mins.</i>				
8-86	43.15	46.21	+++	++	++	+++
8-81	43.42	46.58	+	++	+	++
9-32	46.18	48.45	+++	+++	++	+++
9-81*	46.29	48.43	+	+	+	+
9-76*	46.50	49.12	++	++	+	++
8-37	49.55	52.35	++	++	+++	+
X	49.55	52.50	++	++	+	++

* Filtrate from culture of strain K-158A, extremely virulent to rabbits; other rabbits injected with filtrate of S-23, Lancefield strain.

The production of leukocidin by either pneumococci or streptococci has been studied by a number of investigators.^{28,29,30} Little is known concerning the respective chemical properties and potency of these substances. It is, therefore, conceivable that a highly effective staphylococcus leukocidin may be capable of inducing lymphatic blockage as well as death of cells. On the other hand, with the media employed, the toxins of streptococci and pneumococci, while unable to produce lymphatic blockage may, nevertheless, be sufficiently potent to affect leukocytes.

Recent unpublished studies have clearly demonstrated that the local inflammatory reaction, by determining the degree of invasiveness, is an important factor in immunity.³¹ The resistance of the host infected with a virulent microorganism represents the resultant of a number of factors, including among others, the invasiveness and the virulence of the bacteria. The invasive property of a microorganism has often been taken as a criterion of its virulence and *vice versa*.³⁴ Some bacteriologists have, however, recognized that virulence and invasiveness are different properties which are not to be confused and the terms are therefore not to be employed synonymously.³⁵

The factor of invasiveness may be studied as a separate variable by a number of experimental procedures; for example, by interfering with the dissemination of a given virulent microorganism from its site of cutaneous inoculation. This end was attained by the superimposed injection of an inflammatory irritant that causes prompt "walling-off." Such manipulation may delay the dissemination of the virulent microorganism, and even in some cases, apparently allow sufficient time for the local inflammatory reaction to dispose of it in large part. In this way the full effect of virulence, as mani-

fested by massive blood stream invasion and subsequent death, may be delayed, and, in a few cases, even aborted. Nevertheless, there was no indication from these observations that the virulence or the toxic property *per se*, of the pathogenic microorganism had been in any way altered by delaying its invasiveness.³¹

The experiments were set up somewhat as follows: White rabbits were inoculated intracutaneously with varying dosages of a virulent strain of pneumococcus, Type III. This was immediately followed by the introduction of a broth culture of *S. aureus* into the same skin area. It is to be remembered that the latter organism causes rapid "walling-off" of its area of inoculation. When aleuronat or turpentine was employed as the superimposed irritant, similar results were observed as with staphylococci. Control animals received an identical inoculation with virulent pneumococci upon which was superimposed sterile broth, 0.5% saline, or water. None of the latter substances induce lymphatic blockage. All experimental rabbits survived longer than the controls. Two out of 12 animals survived the combined inoculations of virulent pneumococci and staphylococci for over a month. At that time, although both animals were well, one of them was sacrificed. The controls of these two rabbits survived 5 days and 3 days respectively. By comparing and correlating the fixation of a dye at the site of the combined bacterial inoculation with histological findings, it was shown that the increase in survival time of experimental rabbits was entirely referable to the effect of the staphylococcus organism which, by inducing mechanical obstruction in the form of coagulated plasma and fibrinous thrombi in lymphatics, delayed the normal invasiveness of the virulent pneumococci. Blood cultures fully confirmed this interpretation. Whereas 2 or 3 hours following the inoculation of pneumococci in the skin of control rabbits, these organisms were recovered from the blood stream, in the case of experimental animals the virulent organisms were able to penetrate into the circulation not before 13 to 19 hours subsequent to their inoculation. The virulence of the pneumococci was in no way changed by the experimental manipulation. The recovery of pneumococci from the site of skin inoculation of an experimental rabbit injected into a normal animal induced massive infection followed by death several days later. The organisms recovered from the blood of such an animal revealed capsulated pneumococci.

These observations clearly indicate the rôle of the inflammatory reaction in regulating the rapidity of invasiveness of a microorganism and therefore the significance of this factor in grading the immunity or resistance of the host, but in no way does the rate of dissemination alter the virulence *per se* of the bacteria which still remains a most important factor in evaluating resistance. Virulence and invasiveness are therefore regarded as two separate variables in studying problems of immunity.

Conclusion. I have called your attention to the dynamics of the inflammatory reaction in its relation to immunity. Powerfully necrotizing irritants produce as a result of an increase in capillary permeability and of lymphatic damage, an extremely prompt reaction, perhaps best termed *fixation*. By this process, the area of injury is mechanically circumscribed and the dissemination of the irritant is prevented. *S. aureus* is an example of such a bacterial irritant.¹² Aleuronat is a chemical irritant of similar potency.¹ Mild irritants, on the other hand, produce only a delayed reaction, thus allowing relatively free penetration of the irritant into the circulation for a considerable interval of time. Occlusion of the draining lymphatics in such instances often takes place as late as two days subsequently to the inoculation of the irritant. Hemolytic streptococci exemplify this type of irritant. Another instance has been recently demonstrated by McMaster and Hudack³² who showed that up to 48 hours following a mere skin incision or local burn, lymph drainage is adequate. Subsequently lymphatics failed to convey effectively materials contained in them. The intensity of fixation is found frequently to be parallel to the extent of inflammatory edema. This would suggest that the local swelling is at least in part the result of blockage to normal lymphatic drainage which is thus unable to cope adequately with the excess outpouring of plasma from the capillaries at the site of inflammation.

In relatively large suppurating or acutely inflamed areas the reaction of fixation may occur as early as 30 minutes after the injection of an irritant. This prompt response allows a definite interval of time for the relatively sluggish leukocytes to assemble at the site of inflammation for the purpose of phagocytosis. The neutrophils appear first, to be displaced subsequently by the macrophages. This cytological sequence, as recently demonstrated, is evidently conditioned by changes in the local hydrogen-ion concentration. With the developing local acidosis at the site of an acute inflammation, the predominating cell of the exudate shifts from the neutrophil to the mononuclear phagocytic type.³³ It is conceivable that the mechanism of suppuration is closely associated, perhaps through an activation of autolytic tissue enzymes, with the local increase in the hydrogen-ion concentration of an inflamed area. Studies are now in progress in an attempt to clarify this problem.

The reaction of *fixation* by mechanically circumscribing the irritant in the earliest phase of the acute inflammatory reaction, plays a definite rôle in immunity, for it protects the organism as a whole at the expense of local injury. The reason for the disastrous effects resulting from untimely surgical interference with such an effective inflammatory barrier, as described above, and which is encountered, for example, in the staphylococcus boil or the anthrax carbuncle, is quite obvious and needs no particular emphasis in view of the foregoing discussion.

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- (Titles have been omitted for sake of brevity.)

VARIATIONS IN THE GASTRIC MUCOSA IN PERNICIOUS ANEMIA: GASTROSCOPIC, SURGICAL AND ROENTGENOLOGIC OBSERVATIONS.

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SINCE the early studies of Fenwick,¹ Cahn and von Mering,² and the subsequent observations of Faber and Bloch,³ it has been recognized that there are apparently histologic changes in the gastric

mucosa which are invariably associated with the disease, pernicious anemia. These changes, first described in detail by Faber and Bloch, consist in a diffuse inflammatory process leading to the destruction and atrophy of the gastric glands, most striking in the cardia and decreasing in severity toward the pyloric end of the stomach. Achylia, an almost invariable accompaniment of pernicious anemia, is also frequently to be found in the conditions known as atrophic and hypertrophic gastritis. Clinical studies such as those of Hurst⁴ and Miller⁵ have but served to emphasize the importance of the association between abnormalities of gastric secretion and the presence of a local inflammatory process showing at times hypertrophy and at other times atrophy of the gastric mucosa, and usually designated as chronic gastritis. According to Faber⁶ secretory failure probably exists long before there are any marked changes in the gastric mucosa and submucosa indicative of glandular atrophy and characteristic of any chronic inflammatory process.

In cases of pernicious anemia it has been shown repeatedly, as in the reports of Hurst and others, that even after successful liver therapy there is rarely any change in the accompanying anacidity. Usually such observers have considered that the gastritis with its associated secretory changes represents a primary rather than a secondary condition and persists despite any successful treatment of the clinical syndrome known as pernicious anemia. This is also suggested by the studies of Castle,⁷ which demonstrated a defective and usually completely absent secretion of the intrinsic factor in gastric juice necessary for normal maturation of the red cells. The histologic studies of Faber and others have been supplemented by direct gastroscopic observations by Henning,⁸ Schindler,⁹ Benedict¹⁰ and others. All of these observers agree that in pernicious anemia there exists an atrophy of the gastric mucosa as an invariable finding. A quotation from Henning's recent monograph⁸ on inflammation of the stomach, which may be used for comparison with the observations to be reported, is given: "I have seen diffuse atrophy of the mucous membrane in all cases of pernicious anemia examined up to the present time, in many cases of complete achylia and carcinoma of the stomach and also in many resected stomachs. The picture of complete atrophy is extraordinarily impressive. The color of the mucous membrane is grayish yellow to grayish green. (The color of normal gastric mucous membrane is red.)* This color tone may be striking only when the stomach is entirely unfolded by marked inflation. By this method even normal or even delicate folds are so perfectly stretched that as a rule they appear entirely smooth or even finely granular. As a further characteristic one notices a strikingly distinct appearance of the coarser and even the finest bloodvessels. The larger bloodvessels arch their course

* Authors' note.

upward along the thin mucous membrane. Since, as a rule, it occurs in small stomachs of the steer horn type there exists a good possibility for observing it also at the pylorus. . . . * One clearly recognizes in the endoscopic photograph the dark appearing vessels in the bright mucous membranes. In the microphotograph of the histological specimen one observes the characteristic disappearance of gastric glands, complete atrophy of specific glands, goblet cell metaplasia and cellular infiltration of the interstitial tissues."

Henning believes that "the sharp outline of the vessels and their distinct arching over in a brilliant mucous membrane of grayish yellow color is decisive" as a diagnostic criterion of atrophic gastritis. He thinks that such a finding is invariably seen in pernicious anemia.

It is important to point out that all the observations noted above have been made on patients suffering from a typical relapse of pernicious anemia. With the exception of studies on gastric secretion, no observations on the stomach itself have been made during remissions following successful treatment of the disease. It is the purpose of this communication to describe the gastroscopic, roentgenologic and other changes occurring in patients suffering from pernicious anemia during a typical relapse of the disease and subsequent observations made during a typical remission. Such observations, although few in number, we believe to be of sufficient importance to warrant reporting in detail, with the hope that they may further stimulate the study of what must be considered as fundamental variations in gastric physiology.

Clinical Material.—The patients were typical cases of pernicious anemia as proved by all of the usual diagnostic criteria. Patient 1 has been under continuous observation since 1917. The 4 remaining patients have been followed by us at this hospital over periods ranging from 1 to 8 years. All 5 of the patients gave typical responses to liver therapy. Gastroscopic examinations were carried out with the flexible Schindler gastroscope and roentgenologic examinations were made using the compression technique (Berg¹¹) for the demonstration of the mucosal markings of the stomach. In 3 instances examinations of the stomach were made during a typical relapse and, in addition, subsequent examinations were made at or near the height of a remission. The gastroscopist and roentgenologist both paid particular attention to the prominence, thickening and tortuosity of the gastric rugæ, or to their absence. In 2 instances direct observation of the stomach at operation replaced the initial gastroscopic examination.

Cases. Patient 1, a white man, aged 58, with a negative past history, was first bothered by a sore tongue in 1917, the symptoms persisting for 2 years. In 1919 he entered this hospital with a typical picture of pernicious

* A colored plate showing the gastroscopic appearance of an atrophic stomach can be found in Henning's monograph.

anemia. There had been epigastric pain for the preceding year and the patient had lost 14 pounds in weight.

Physical Examination. Nothing abnormal was noted with the exception of sallow pallor and a smooth, red, sore-looking tongue.

Laboratory Examinations. Negative except for blood and gastric analysis. The red count was 2,640,000 and the blood smear showed the typical changes characteristic of pernicious anemia. There was marked macrocytosis with striking inequality in size and shape of the red cells which were well filled with hemoglobin. The blood platelets were somewhat diminished. A gastric analysis after an Ewald test meal showed no free hydrochloric acid in any of the specimens collected.

Repeated Roentgen rays taken at this time showed suggestive changes in the antrum of the stomach on 2 occasions, although a third examination showed no evidence of disease.

The patient was discharged unrelieved with a diagnosis of pernicious anemia.

A spontaneous remission occurred and the patient remained in good health until 1922, at which time there was a typical relapse with sore tongue, loss of weight, and anemia. At this time the patient was advised to eat large quantities of red meat, which he did for a period of about 2 months. A sharp, spontaneous remission again occurred, due probably to the large quantities of meat ingested and the fact, noted later, that presumably he had a small amount of Castle's intrinsic factor in his gastric secretion. Since the advent of liver therapy the patient has taken liver or liver extract at frequent intervals, maintaining the normal level of his blood without difficulty without the recurrence of the stomatitis, paresthesias, or other symptoms, until 1934 when a slight relapse occurred which was relieved by the regular addition of liver to his diet for a short time.

It is of some interest that a second gastric analysis performed with histamin, in 1925, showed a maximum free titratable acidity of 25 cc. tenth-normal acid at the end of 1 hour. It is probable, as already suggested, that the presence of moderate amounts of free hydrochloric acid was associated with at least minimal amounts of Castle's intrinsic substance. Such a fact would explain the relative ease with which the patient maintained himself free of symptoms of the disease with only moderate therapeutic measures. Because of the finding of free hydrochloric acid after histamin the case was reviewed, but it was the opinion of Dr. George Minot as well as ourselves that there was no reason to doubt the diagnosis of pernicious anemia.

During the past 3 or 4 years there has been mild, indefinite epigastric distress and belching, usually associated with fatigue or indiscretions in diet. The day before his second admission on June 29, 1934, the patient felt weak, had generalized abdominal distress and suddenly vomited a large mouthful of free blood. In the next 24 hours there were two more attacks of hematemesis and a tarry stool was passed.

Physical examination on this admission was negative except for pallor and a tongue which was slightly smooth at the edges.

Laboratory Data. Urine negative. Red count, 3,040,000. Hemoglobin, 65%. A blood smear showed slight achromia of the red cells with moderate variation in size and shape. Stool examinations showed evidences of occult blood.

The admission diagnosis was pernicious anemia and probable polyposis.

Ten days after admission all signs of bleeding had subsided. Roentgen rays of the stomach taken at that time showed a small hiatus hernia and apparently a polyp of the antrum.

Gastroscopy showed a moderately pale mucous membrane but not characteristic of complete atrophy of the stomach. No bloodvessels could

be seen. Gastric rugæ were absent. Only glimpses were obtained of the antrum where there appeared to be a thickening of the mucous membrane which might have been a polyp.

Because it was felt that the hemorrhage was due to a polyp of the stomach, surgery was decided upon and operation was performed 1 month after admission. On the lesser curvature a hard nodule was felt which, on resection, proved to be a lymph node. Frozen section showed carcinomatous involvement of a very malignant nature. The stomach was opened about 3 inches from the pylorus and on exploration of the greater curvature a small carcinoma was found and local resection was performed.

Subsequent examination of the resected stomach and the lymph node showed adenocarcinoma. Sections of the fundus adjacent to the tumor showed dilatation of some of the tubules, but for the most part the gastric tissue appeared normal. There appeared to be no atrophy. The parietal cells were present in normal numbers. In the sections studied there was no evidence of gastritis.

Convalescence was uneventful and since the operation the patient has gained weight and strength and has been symptom-free. He has been working steadily and since November, 1934, his blood has returned to and remained at an absolutely normal level. Gastrosocopy performed in March, 1935, showed slight apparent hypertrophy of the gastric mucosa without any evidence of polyps or of metastases. A Roentgen ray examination made at the same time, and again in June, 1935, revealed no evidence of metastases or of gastritis.

The findings in this case are of particular interest when contrasted with those made on the 4 following patients, 3 of whom were examined in a typical relapse as well as during a remission. In this particular instance the gastroscopic and roentgenologic examinations were made to determine the cause of hematemesis during a period in which the patient had no symptoms of pernicious anemia.

Patient 2, a white man, aged 57, with an irrelevant past history, 8 years before admission began to notice subxiphoid distress immediately after meals associated with very irregular eating habits. This was relieved by induced vomiting. A return to regular eating habits relieved his symptoms for the most part with the exception of occasional attacks of mild indigestion always associated with fatigue or irregularity in eating. One year before admission the patient noticed easy fatigability culminating in an attack of pain in both axillæ and upper arms, particularly on the left side. He was seen by a consultant who made a diagnosis of probable coronary disease and at the same time noted that he was slightly jaundiced. After 5 weeks in bed the patient had a sudden attack of right upper quadrant pain with an increase in jaundice and residual soreness in the abdomen. A second consultant diagnosed cholelithiasis. Continued rest for the next few months resulted in a clearing of the jaundice, but on resuming some physical activity the patient noticed extreme fatigability, dyspnea and substernal distress on slight exertion. Indigestion and loss of appetite were prominent symptoms for the next 4 months with some nausea and a loss of about 8 pounds. Just before admission he noticed some soreness of his mouth and "canker sores" on his tongue. He was admitted to the hospital for study on September 26, 1934, and an immediate diagnosis of pernicious anemia was made, based on the appearance of the patient and further proved by examination of the blood.

Physical examination showed a sallow, pale individual with slight icterus of the scleræ. The tongue was slightly smooth around the edges. Exam-

ination was otherwise essentially negative except that the liver was easily palpable 6 cm. below the costal margin in the right midclavicular line.

Laboratory Data. Urine and stools negative. Red count, 2,240,000. Hemoglobin, 45% (Tallqvist). The stained smear of the red blood cells was characteristic of pernicious anemia. Gastric analysis with histamin showed complete anacidity.

Roentgen ray examination of the stomach showed what appeared to be several large polyps along the greater curvature and a striking increase in all the gastric rugæ. A radiograph of the gall bladder area showed shadows characteristic of biliary calculi.

An electrocardiogram was normal.

Because of the above findings a diagnosis of pernicious anemia, gastric polypi, with possible carcinomatous degeneration, and cholelithiasis was made. It was felt that the symptoms of coronary disease were fundamentally due to the marked anemia and that operative procedures were justified if the blood could be brought back to normal. Intensive parenteral liver therapy was initiated with a typical response in the reticulocytes which rose to 17.3% in 1 week, and a rise in the red count at the end of 1 month to 4,020,000. The failure to obtain a more satisfactory rise in the red count was due to the fact that there was an interval attack of acute cholecystitis with fever, chill, leukocytosis, increased jaundice and sharply localized tenderness over the gall bladder area. At the end of 1 month it was decided that operation on the gall bladder was necessary, although we had at first hoped to do a gastric resection.

At operation a subacute cholecystitis was found and a thick-walled, ulcerated gall bladder containing many pigmented stones was removed. Because of the condition of the patient it was deemed unwise to attempt a large gastric resection, but the stomach was opened and two large polypoid tumors which had been localized by Roentgen ray were removed with resection of a broad base. The remainder of the stomach was inspected carefully and showed a very dark red mucosa with marked hypertrophy of all the rugæ, which at times were so thickened as to present verrucous enlargements that had the appearance of polypi or tumor masses. The appearance was characteristic of hypertrophic gastritis. Drainage of the gall bladder area was instituted and the abdomen closed. The patient had an uneventful recovery and was discharged from the hospital 1 month after admission with a red count of 4,670,000 and a hemoglobin of 75%. Clinically he was symptom-free and on moderate exertion had no cardiac symptoms whatever.

Microscopic examination of the polypi removed from the stomach showed evidence of active growth. The gland tubules were large and irregular in size and shape. There was no evidence of invasion but it was considered as potentially malignant. A subsequent examination of serial sections of the base showed definite invasion by tumor in the pedicle of the growth below the muscularis mucosa and a diagnosis of adenocarcinoma was made.

Two months after discharge the patient reentered the hospital for gastroscopy. On physical examination the patient showed a profound change, with a complete absence of pallor and a return to normal weight. The liver which previously had been definitely enlarged was no longer palpable, and the patient stated that he felt better than he had for years and had no digestive disturbances. His red count was 4,770,000. The blood smear showed no sign of abnormality of the red cells.

Gastroscopy showed a mucous membrane of normal color with apparently normal gastric markings. There was no suggestion of atrophy and very questionable hypertrophy of the rugæ. Roentgen ray findings at that time showed much less thickening of the gastric mucosa than had been noted on previous films. The polyp previously described could not be

demonstrated. There was no evidence of recurrence of any carcinomatous process and the appearance was that of an active gastritis.

Four months after the operation the patient had more than regained his lost weight, was working and felt perfectly well. The gastroscopic examination at this time showed a normal color of the mucous membranes with a few bright red areas between the folds and one diffuse area suggesting submucous hemorrhage. The rugæ were present and appeared normal. There was no evidence of recurrence of the tumor or of polypoid formation. The appearance was that of a mild superficial gastritis but did not suggest atrophy. Roentgen ray findings at this time showed very little change from the previous examination. There was no evidence of recurrence of malignancy.

When last seen, 9 months after the operation, the patient was still in excellent health and 8 pounds heavier than he had ever been.

Patient 3, a white man, aged 62, past history irrelevant, 6 months before admission noticed weakness and shortness of breath on exertion with swelling of his ankles at the end of the day, pallor and questionable jaundice. During the latter part of his present illness he developed numbness and tingling of his hands and toes. Anorexia, constipation, nausea and vomiting were important symptoms without loss of weight. He was told that he was anemic and was treated with iron with temporary relief of symptoms except for the paresthesias which persisted. One month before admission all his symptoms returned. He was seen in the Outpatient Department where Roentgen rays were taken and a blood examination was done. A diagnosis of pernicious anemia was made. The Roentgen ray examination showed an irregular filling defect with evidence of crater formation involving the lower half of the stomach. The findings were thought to be those of carcinoma involving the lower half of the stomach.

Physical Examination. On admission the patient showed a striking sallow pallor, otherwise there were no physical findings of importance.

Laboratory Data. Urine and stool examinations were negative. Red count, 1,380,000. Hemoglobin, 45% (Tallqvist). The stained smear of the red cells was characteristic of pernicious anemia. Gastric analysis with histamin showed complete anacidity.

Reexamination of the stomach by Roentgen ray confirmed the previous findings and showed a large defect in the pyloric end of the stomach. Gastroscopy showed a very pale, thin mucous membrane throughout the entire stomach. Numerous small bloodvessels could be very well seen. Normal rugæ were almost entirely absent. On the lesser curvature and posterior wall in the antrum of the stomach there was a rounded elevated red lesion, smooth in contour, attached by a broad base. The lesion was about 7 to 8 cm. in diameter. It was thought that the appearance of the mucosa was absolutely typical of the atrophy seen in pernicious anemia in a relapse and it was also felt that probably the lesion was a benign polyp, although there was a definite chance of early malignant degeneration.

It was decided to resort to surgery as soon as the patient's condition permitted and after 2 transfusions operation was performed. The tumor was easily palpated and on opening the stomach a long tongue-like polyp about 6 inches in length and ulcerated in two places was seen on the posterior wall about one-third of the way up from the pylorus. This was excised with a wide margin around the base. Microscopic examination of the tumor showed no evidence of malignancy and it was diagnosed as a benign gastric polyp. Examination of the surrounding mucosa showed some exaggeration of depth and tortuosity of the superficial portion of the antral glands, otherwise they were not remarkable. The cells lining the deepest portion of the pyloric glands were low and the lumina were large.

The patient had an uneventful convalescence and on discharge, 7 weeks after admission, his red count had risen to a level of 3,900,000 with a hemoglobin of 70% on adequate liver therapy.

He was readmitted to the hospital 5 months later for further treatment of his pernicious anemia, intensive treatment having been discontinued through a misunderstanding on the part of the patient. He had been perfectly well up to 1 month before admission, when his symptoms of weakness and shortness of breath returned. On admission his red count was 1,700,000 with a hemoglobin of 45%.

Gastroscopic examination was repeated and at this time the mucosa presented a very different appearance from that of the previous examination. The color was moderately pale in some areas, in other areas the color was approximately normal, the whole appearance being that of a rather blotchy dark and light pink surface. Rugæ were present along the greater curvature and were somewhat irregular but appeared nearly normal in size. Near the antrum there was a pseudopolypoid arrangement. The gastroscopist felt that there was a chronic gastritis present in a transitional stage from the previously described atrophic type. He felt it was tending towards the verrucous or hypertrophic type. Intensive liver therapy was instituted and there was prompt response showing a rise in the red cells to 2,500,000 and the hemoglobin to 60%.

A subsequent gastroscopy 2 months later showed a mucous membrane absolutely normal in color with no evidence of atrophy. There appeared to be a very superficial gastritis without obvious evidence of hypertrophy. The red count at this time was 3,660,000 with a hemoglobin of 65 to 70%.

Patient 4, a white woman, aged 70, past history irrelevant, first noted easy fatigability in 1925 with associated palpitation on exertion. One year later there was mild indigestion with anorexia and a loss of 25 pounds in weight in the following 2 years, at the end of which time she was admitted to the hospital. There was some intermittent soreness of the tongue. On admission her presenting symptom was diarrhea of 10 days' duration without blood or cramps.

Physical Examination. Essentially negative except for pallor and loss of weight.

Laboratory Data. Urine and stool examinations negative. Red blood cells, 2,000,000. Hemoglobin, 60%. Stained smear of the red blood cells was consistent with pernicious anemia with moderate macrocytosis. Gastric analysis showed frank blood in all specimens. There was no free hydrochloric acid after an Ewald test meal and only 5 cc. of total acid as a maximum secretion.

Roentgen ray examination showed well defined mottling involving the pyloric end of the stomach and the duodenal cap. These findings were interpreted as indicative of polyposis of the stomach and first portion of the duodenum.

A diagnosis of pernicious anemia and gastric polyposis was made and the patient was treated with liver by mouth with a rise in the red count to 3,400,000 in 4 weeks. The patient was then discharged from the hospital on a dosage of 300 gm. of whole liver by mouth daily and showed gradual but steady improvement. Her appetite remained only fair, however, and the diarrhea was not entirely controlled. In addition there were several attacks of acute "indigestion" with some epigastric pain lasting for several hours without chills, fever or jaundice.

She was admitted to the hospital again after a period of 6 weeks, at which time the physical examination was the same as on the first admission. The red count was 4,800,000, hemoglobin, 75%, and a practically normal blood smear. Repetition of the gastric analysis again showed gross blood and no free hydrochloric acid after a test meal, although there was a max-

imum total acidity at this time of 24 cc. tenth-normal acid. Stool examinations gave a strong test of occult blood.

A second Roentgen ray examination was interpreted as confirming the previous diagnosis of polyposis of the pyloric end of the stomach.

The patient was discharged without additional treatment and was followed in the Outpatient Department for the next 4 months, at the end of which time she entered the hospital for the purpose of operation. During this 4-month period she was bothered by a good deal of gas and distention accompanied by a burning pain of moderate severity occurring 2 hours after meals and relieved by cold water. Diarrhea of a moderate severity had been an intermittent symptom.

Physical examination at this time revealed an irregular tender mass under the right costal margin which was thought to be the liver.

The blood examination showed a red count of 5,500,000 with a hemoglobin of 90%. The stools again showed evidence of occult bleeding and the gastric analysis remained unchanged.

Operation was decided upon and was performed at this time. The stomach was opened by a longitudinal incision and appeared everywhere to be covered with small polyps, the largest of these were about 3 inches in diameter. In addition the rugæ in several places seemed to be thickened as if edematous. The whole area from the pylorus to the cardia was "red and inflamed." A section of the stomach was taken for microscopic examination but it was decided that nothing short of a complete gastrectomy would offer a solution and this was deemed inadvisable. Accordingly, no further surgical procedure was performed: The biopsy showed lymphoid cell infiltration and areas of infiltration in the mucous membrane and wall. A diagnosis of a chronic inflammatory process was made.

Four years later the patient came to the Outpatient Department in response to a letter. She said she had been very much better since the operation. There had been no loss of weight and the only symptoms were those of slight epigastric distress after eating without nausea or vomiting. She was working full time and was on a liberal unrestricted diet. In addition she had been taking dilute hydrochloric acid and 2 pounds of raw liver a week. At this time the stomach was examined with small amounts of barium and no constant filling defects could be seen which could be interpreted as polyps. There were a few 0.5 cm. shadows between the greater and lesser curvatures which possibly could be interpreted as polyps. There were no defects in contour or interference with peristaltic movements and no disturbance of gastric rugæ. The note was made that this Roentgen ray examination showed definite improvement over the findings of 5 years before. Another Roentgen ray was taken a month later with more careful technique. The report was that the only definite variation from the normal was marked thickening of the gastric rugæ. It was thought that the deformity was quite typical of hypertrophic gastritis.

Two years later the patient was seen again and said that she felt well and strong. Treatment had been the same throughout this 2-year period with the blood remaining at a normal level. Roentgen rays taken of the stomach by compression technique at this time showed no positive variation from normal except for some possible thickening of the mucosa about the pyloric valve on the duodenal side.

A gastroscopy was done at this time. The rugæ appeared rather large and slightly tortuous at first but with inflation they almost disappeared and the mucous membrane appeared smooth and glistening. The color was approximately normal. No bloodvessels were seen and there was not the pallor seen in advanced pernicious anemia. No ulcerations, erosions or excrescences were noted. The findings were thought to be those of a nearly normal stomach.

Patient 5, a white man, aged 46, with a past history essentially negative except for dental sepsis, for 6 months had noted anorexia, slight nausea before eating, and for 1 month before admission dyspnea on exertion with substernal tightness. At the same time he noted numbness of his hands and legs and marked pallor. There was a loss of 10 pounds during the 6 months.

Physical Examination. There was moderate icterus, marked pallor, dental sepsis and a slight diminution of vibration sense over the right shin. Otherwise the examination was essentially negative.

Laboratory Data. The urine and stool examinations were essentially negative. Examination of the blood showed a red count of 1,270,000 with a hemoglobin of 40%. The smear was characteristic of that seen in pernicious anemia. Gastric analysis showed complete anacidity with histamin.

Roentgen ray examination showed that the gastric rugæ were slightly more prominent than normal.

Gastrosopic examination showed that the mucous membranes were much paler than usual, particularly in the fundus where a network of bloodvessels was seen. In some areas the mucosa was of a fairly normal red color and the entire appearance was that of a rather blotchy white and pink appearance. On the greater curvature near the antrum there was a definite nodular protuberance 2 cm. long. It was thought that the findings were those of an atrophic gastritis with probable pseudopolyposis.

Intensive liver therapy was instituted at once with a gradual rise in the red count so that 3 months later the red count was 4,690,000. The relatively slow rise in the number of red cells was due to the fact that during the course of the treatment several fractions of liver extract that were being used were found to be of relatively low potency. With the rise in the red count all symptoms disappeared.

A second gastrosopic examination was made 2 months after admission. At this time the color of the mucous membrane was practically normal. The mucosa appeared somewhat granular in places, indicating a mild gastritis. On the greater curvature there was a small smooth swelling which did not disappear on inflation and might have been either a true polyp or a pseudopolyp. High up on the posterior wall there was an area of increased redness which appeared to be a submucous hemorrhage. There was no doubt that the appearance of the mucous membrane had improved in a striking fashion since the first examination, and in no sense could be classified at this time as that of an atrophic gastritis.

Discussion. From the preceding observations several facts of interest are to be noted. By comparison with the accepted description of gastric atrophy, as previously given, typical atrophy was noted at gastroscopy in 2 of the 5 cases, Patients 3 and 5, at the first examination, and slight atrophic changes were to be seen in one other, Patient 1. The 2 patients showing marked atrophy were at the time in a typical relapse of the disease with red blood counts under 1.5 million. In the third case, Patient 1, having a red count of 3.6 million, there was very slight evidence of atrophy at the time of gastroscopy. The other 2 patients, when examined with a gastroscope, showed no evidence of an atrophic process, the red counts at the time of this examination were 5.5 and 4 million red cells, respectively. It would seem to follow that gross atrophic changes in pernicious anemia need be expected only in those patients suffering from a typical relapse. That the gross appearance of atrophy may be absent even during the period of relapse is appar-

ently true from the fact that Patient 2 showed an extremely hypertrophied, inflamed stomach at the time of his operation, at which time he was just beginning to show a proper response to liver therapy.

From gastroscopic observations, therefore, it is obvious that, contrary to the generally accepted views, atrophy of the stomach is not an invariable accompaniment of pernicious anemia. Following successful treatment of the anemia by appropriate liver therapy, later gastroscopic examinations showed striking changes in the appearance of the stomach in each instance. In the case of Patients 3 and 5, where previously there had been a characteristic appearance of marked gastric atrophy, all suggestion of an atrophic process had disappeared in the course of 5 months and 2 months, respectively. In the place of a pale, smooth mucosa with easily visible bloodvessels and an absence of the rugæ there was a complete return to normal color, the rugæ appeared normal, no bloodvessels could be distinguished, and the appearance was that of a mild superficial gastritis. In Patient 1 the changes were less striking, inasmuch as the original appearance, even after the pernicious anemia had been present for years, was that of only slight or questionable atrophy, but they were of the same nature as those just described. This was not surprising in view of the fact that at the first gastroscopic examination Patient 1 was not in a relapse but was suffering from a post-hemorrhagic anemia. In those patients showing no gross evidence of atrophy at the first examination there was also a marked change following a course of specific therapy of the previous anemia. In both Patient 2 and Patient 4 the initial observations were those of marked hypertrophic gastritis. Following liver therapy there was a gradual but striking return to a normal appearance.

The operative findings in 3 of the 4 patients, Patients 1, 2 and 4, who came to surgery were similar. Unfortunately no adequate description of the stomach was given after operation in Patient 3. On inspection of the stomach in the 3 cases noted there was no gross evidence of atrophy, but the appearance was rather one of a diffuse inflammatory process with marked hypertrophy of the rugæ. In 2 cases, Patients 2 and 4, the rugæ were so thickened it was impossible to determine whether polyps were present or merely a thickening of the mucosa (pseudopolyps). None of the 3 patients was in a severe relapse when operated upon, the red counts being 3.6, 5.5 and 4 millions, respectively. In the case of Patient 1, the lowered red count was due fundamentally to a recent gastric hemorrhage from a polypoid tumor in the stomach.

Microscopic examination of gastric tissue removed at operation confirmed the observations already noted. The pieces of tissue examined showed no evidence of an atrophic process in any of the cases, although there was a marked inflammatory process with

lymphoid cell infiltration and hemorrhage in the mucosa and submucosa in two instances.

The Roentgen ray examinations constituted an interesting check on our other observations but gave much less accurate information than that obtained either by gastroscopy or by direct examination at operation. In general it can be said that the chief value derived from such examinations was that of noting progress in a given case. This was shown in the set of observations obtained in Patient 4. In 1927 and 1928 three observations were made, all showing marked hypertrophy of the gastric rugæ which was interpreted as meaning a diffuse polyposis of the stomach. Examination of the stomach at operation in 1928 apparently confirmed these observations, although microscopic examination of the biopsy specimen revealed only the chronic inflammatory changes present in pseudopolypoid formation. After $5\frac{1}{2}$ years of constant liver therapy, 2 further Roentgen ray studies were made and a year later a final examination was made. At the latter examination there was a change of such a degree that in the final Roentgen ray it was impossible to find any positive variation from the normal except for some apparent thickening of the mucosa on the duodenal side of the pylorus. Gastroscopy performed at the time of the last examination was essentially normal. Associated with these changes there had been a gradual and steady disappearance of all gastric symptoms. The discrepancy between gastroscopic and roentgenologic findings has been noted by others and in making an accurate diagnosis of atrophic or hypertrophic gastritis, polypoid formation and the like, it is undoubtedly true that gastroscopy offers the most valuable diagnostic aid that we have.

It remains to be said that although atrophy was absent in all 5 patients when the anemia was responding to proper treatment, there was present in every case gastroscopic evidence of a definite chronic gastritis.

Repeated examination of the gastric secretion in several of the patients revealed no return of hydrochloric acid where previously achlorhydria had been present. Such a finding was, of course, to be expected and has been discussed frequently by others. According to Faber, in older patients, regardless of the underlying cause, achlorhydria when once established rarely shows any tendency to change, even where there is a complete disappearance of all associated symptoms. He also made the important observation, which is applicable to the cases under discussion, that achlorhydria may be present in the complete absence of any microscopic evidence of gastritis and may be considered as one of the earliest symptoms of the disease in its chronic atrophic form.

In view of the nature of the preceding observations, one cannot escape the conclusion that adequate treatment of pernicious anemia not only permits a proper maturation of red cells but also is asso-

ciated with a subsidence of the inflammatory process in the stomach itself and the disappearance of the atrophic process. This was particularly marked in Patients 3 and 5 in whom there had been striking atrophy of the mucosa at the early examinations made during a relapse, with recovery to an almost normal appearing mucous membrane after as short a period as 2 months of intensive treatment. In the case of Patient 3 a resection of gastric tissue was done 1 month after gastroscopy had been performed and liver therapy had been instituted. At the time of this gastroscopy there was extreme atrophy which corresponded in every way to Henning's description previously quoted. The microscopic appearance of the gastric tissue removed at operation 1 month later showed very little evidence of an atrophic process. There was some exaggeration of the depth and tortuosity of the superficial portions of the antral glands and the cells lining the deepest portions of the pyloric glands were low.

The striking changes between the original observations of extreme atrophy and the subsequent observations showing almost normal gastric mucous membrane were clearly associated with clinical improvement in the patient's condition and a corresponding rise in the red count. This apparent change from a very atrophic mucosa to a normal one might conceivably be the result of an improvement in the anemia with coincident improvement in the local blood supply. It would seem more logical, however, to believe that the changes noted in the gastric mucous membrane were of the same nature as those frequently observed in the tongue. It is a well known clinical fact that the glossitis associated with pernicious anemia, with its more or less complete obliteration of the normal papillæ, undergoes a profound change in many cases following intensive specific therapy. Not infrequently the papillæ return and the smooth appearance of the tongue completely disappears as the remission progresses. It is not at all improbable in our opinion that much of the gastric atrophy noted in pernicious anemia by various observers represents an atrophy of the mucous membranes due fundamentally to a specific deficiency rather than to a chronic gastritis. The rapid return to normal which we have observed may well represent an epithelial change associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process. One is even tempted to speculate as to the possibility that at times the gastritis associated with pernicious anemia may follow the degenerative changes in the epithelium rather than initiate them. By this statement we do not infer that chronic gastritis may not be a causal factor in certain cases of pernicious anemia. The histories of several of the patients discussed above suggest very definitely that chronic gastric irrita-

tion existed for some time before the development of pernicious anemia.

It is of interest that, as in the cases showing marked atrophy, so in those with striking hypertrophy (Patients 2 and 4) there was a return to a normal appearing mucous membrane after proper treatment. In the case of those patients with hypertrophic changes, the return to normal involved a longer period of time. It is quite probable that, in the presence of a hypertrophic gastritis of long duration, the response to liver therapy involves not only a specific response to the active principle needed in the treatment of pernicious anemia but also a gradual subsidence of a definite chronic gastritis. In any event, there appears to be little room for doubt that the successful treatment of pernicious anemia with the active principle contained in liver may be followed by the subsidence of any underlying gastritis and a disappearance of associated hypertrophic or atrophic changes in the gastric mucous membrane.

Summary. 1. Five cases of pernicious anemia are presented with special reference to the appearance of the stomach before and after successful treatment of the disease. Observations of the stomach were made by gastroscopic and roentgenologic examination, by direct observation at laparotomy and by histologic examination of biopsy material.

2. Evidence is presented which we believe indicates that, contrary to most observers, atrophy of the stomach occurs particularly during a relapse and not as an invariable accompaniment of the disease.

3. Evidences of hypertrophic gastritis have been observed by Roentgen ray during a relapse and also during the early stages of a remission.

4. Following specific therapy of the pernicious anemia, evidences of atrophy and hypertrophy of the stomach have both tended to disappear.

5. We suggest that the change from an appearance of atrophy to that of a normal gastric mucosa frequently represents an epithelial change associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process.

6. We believe that the apparent return to normal from a grossly hypertrophic condition of the gastric mucous membrane represents a subsidence of a chronic gastritis.

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DISTRIBUTION OF THE ERYTHROCYTE POPULATION IN REGARD TO DIAMETERS AND OSMOTIC RESISTANCE IN SPLENECTOMIZED CASES OF HEMOLYTIC ICTERUS.

A CONTRIBUTION TO AN UNDERSTANDING OF THE PATHOGENESIS OF THE DISEASE.

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AND

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THE thesis upheld by Italian authors, and especially by Micheli and Banti, that the spleen holds a central position in the pathogenesis of the primary hemolytic splenomegalies, has been more and more confirmed as our knowledge about this interesting chapter of pathology has become more accurate. Today, therefore, it may be recognized as highly probable that the *primum movens* of such splenomegalic syndromes is hyperhemolysis.* This statement does not exclude by any means the existence of a constitutional diathesis of the bone marrow toward special kinds of pathologic erythropoiesis, a state of affairs which appears only too probable if one bears in mind the strikingly different modes of erythropoiesis in the primary hemolytic splenomegalies and also in other forms of hemolytic anemia, obviously not constitutional, in which the very high percentages of pathologic erythrocytes that are found in the primary forms are far from being attained.

The study of the curves of erythrocyte diameters and of their osmotic resistances, in the period immediately following splenectomy in cases of hemolytic icterus, has shown profound and rapid modifications which we have treated in detail in an article now in press,

* To prevent confusion it should be stated that in many countries the primary defect in hemolytic icterus is thought to lie in an inherited defect of the small, fragile spherocyte. As this article has been translated in our editorial department, the authors should not be held responsible for errors in phraseology.—EDITOR.

changes which we would like briefly to comment upon here. The behavior of these curves until now has lacked precise description, as the hematologic changes, such as those studied by Gamna, in our clinic, refer to a period distant from the operation. If it is possible, as one of our cases demonstrates, to change the production of microcytes by splenectomy in the direction of normocytic erythropoiesis, and to obtain at the same time an almost normal osmotic resistance, it is difficult not to find therein proof that the bone marrow in these patients is not profoundly and constitutionally compromised as regards erythropoiesis.

It is expedient in cases of hemolytic icterus to admit a potential disposition of the marrow toward the production of red cells with an abnormal structure. Such a disposition might be changed into an actual occurrence when the contingencies, such as are present in hemolytic icterus, push the marrow to a prolonged hyperactivity in compensation for the hemolysis.

Let us pass without further ado to the data of our 2 cases which essentially present the following:

Instead of the monoapical curve representing the individual variations of diameters and osmotic resistance of the erythrocytes before splenectomy, there is substituted after the operation a bi-apical curve, a fact which demonstrates the existence of a mixed erythrocyte population. The existence of this mixed population may be, but is not always, transient, tending to evolve into a normocytic population with normal resistance. We need not be astonished, therefore, that the measurements taken some time after splenectomy with methods that are less sensitive than ours do not give the same clear indications.

The 2 cases of hemolytic icterus that we have studied after splenectomy* gave the complete syndrome of splenomegaly (extreme in the first case, the spleen weighing about 1 kg.), acholuric icterus (dating from a few days after birth), anemia with a high color index, diminished diameters and globular resistance.

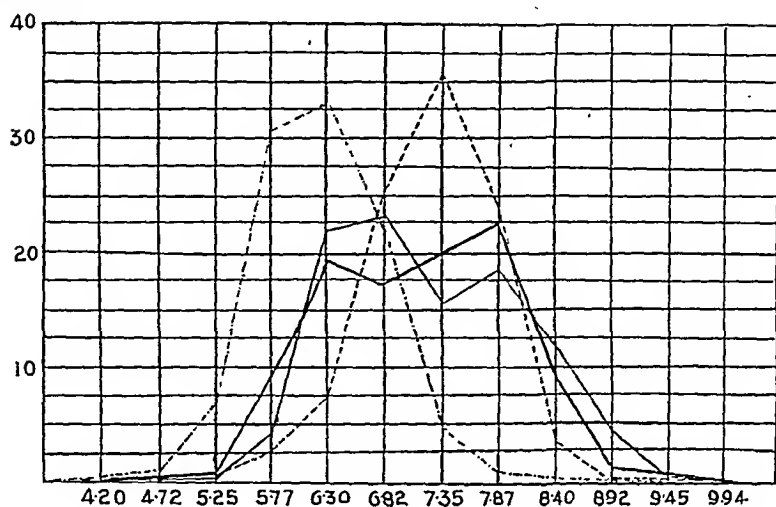
The first case was characterized hematologically (Charts 1 and 2) in the pre-splenectomy period by the fact that the red cells were almost entirely in the form of spheroidal microcytes (93% of the erythrocytes had a diameter less than 7.35μ), and by the fact

* The erythrocytometric and the reticulocytometric curves were obtained from dry spreads that had been fixed in methyl alcohol, making at least 1000 counts for the erythrocytes and several hundred (generally 300) for the reticulocytes. The measurements were made with an optic system of a micrometric value of 1.05μ which, for the normal subject, gives an almost symmetrical monoapical erythrocytometric curve, formed by 8 divisions between 5.77 and 9.45μ and with the following statistical values: $D = 3.7$; $\varphi = 7.6$; $\sigma = 0.57$; $I = -0.01$; and a monoapical reticulocytometric curve formed by 7 divisions between 6.3 and 9.45μ , with the following statistical values: $D = 3.1$; $\varphi = 7.7$; $\sigma = 0.5$ to 0.55 ; I generally positive.

For the curve of osmotic resistance Hamburger's method was used. This also made use of 8 divisions between the concentrations of 1.4% and 0.7% of $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, and is monoapical.

CHART 1.—CURVES OF ERYTHROCYTE DIAMETERS. CASE 1.

% of Cells

Corpuscular diameter in μ

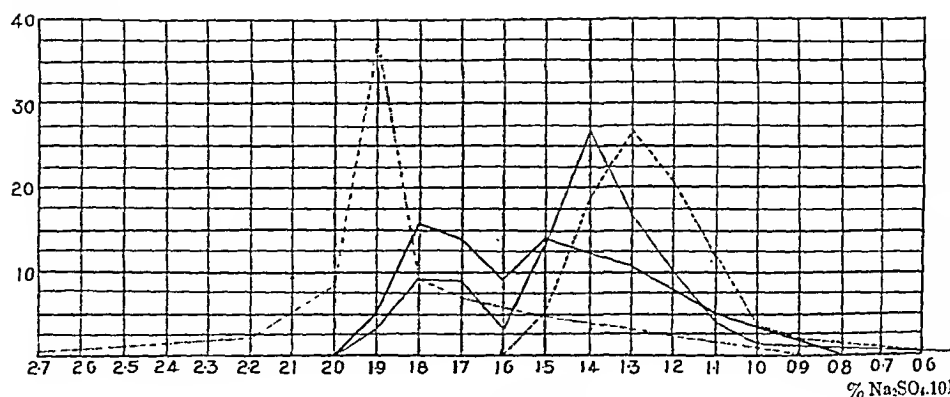
		D	ψ	σ	I
.....	12.IV.34	5,77	6,21	0,59	-0,13
————	25.IV.34	5,77	7,20	0,85	+0,1
—————	30.IV.34	5,25	7,22	0,84	-0,2
-----	23.XI.34	4,72	7,24	0,61	-0,3

Dates.	Hb.	R.B.C., mill. per c.mm.	Color index.	Corpuscular volume, cubic micra.
April 12	68	3.53	0.97	80
25	88	3.60	1.22	
30	88	4.36	1.01	89
June 26	95	4.93	0.96	85
Nov. 23	88	4.65	0.94	97

Splenectomy, April 21, 1934.

CHART 2.—CURVES OF OSMOTIC RESISTANCE OF ERYTHROCYTES. CASE 1.

% Hemolysis

% Na₂SO₄ 10%

.....	12.IV.34
—————	30.IV.34
————	26.IV.34
-----	23.XI.34

that the osmotic resistance was exceptionally low, hemolysis beginning in the solutions very close to the strength of physiologic salt solution. The curve of the erythrocyte diameters was monoapical with the peak at $6.30\ \mu$. It was asymmetrical with a negative index of asymmetry (I), the extent of the variation (D) was greatly increased, the mean diameter (σ) much diminished and the standard deviation (σ) scarcely increased. The curve of reticulocyte diameters was biapical, with a microcytic peak at $6.82\ \mu$ and a normocytic peak at $7.87\ \mu$. The curve of osmotic resistance was monoapical, with the peak at the point of 1.9% of sodium sulphate, producing 40% hemolysis. Beside this peak at 1.9% sodium sulphate, there were found two large groups of cells with resistance either greater or less than 1.9%, so that the extent of variation of the curve was greatly increased. In general the resistance of the erythrocytes was less than that of the normal minimum (1.4%).

Splenectomy produced not only a rapid disappearance of the icterus but a progressive decrease of anemia. Examination of the erythrocytes after the operation showed a rapid decrease of the spheroidal forms and of the spheroidal reticulocytes particularly. Also there appeared a peak of normocytic elements in the curve of erythrocytic diameters in addition to the preëxisting peak of microcytic elements. Thus the curve of erythrocyte diameters became biapical, while the reticulocyte curve remained monoapical, preserving its normocytic peak. The curve of osmotic resistance quickly lost the group of cells with the lowest resistance and became biapical by the formation, on the slant of a peak rather close to that which was already present, of a second peak of more resistant cells, even though still of a resistance below that of a normal minimum.

The normocytic peak of the curve of red cell diameters increased steadily at the expense of the microcytic curve until the curve became monoapical with a normocytic peak. It should be noted, also, that in the curve of osmotic resistance the biapical feature persisted more than in the curve of erythrocytic diameters. Also, while the left-hand peak of the curve maintained a fairly fixed situation, the right-hand peak gradually moved further to the right; in other words, approached a normal position. This had not been actually completed at the time of the last examination; however, there was obtained a hemolysis curve that was fairly near normal, whether this was obtained by the transformation of a biapical to a monoapical by complete disappearance of the left-hand peak, or as judged by the situation of the peak of hemolysis.

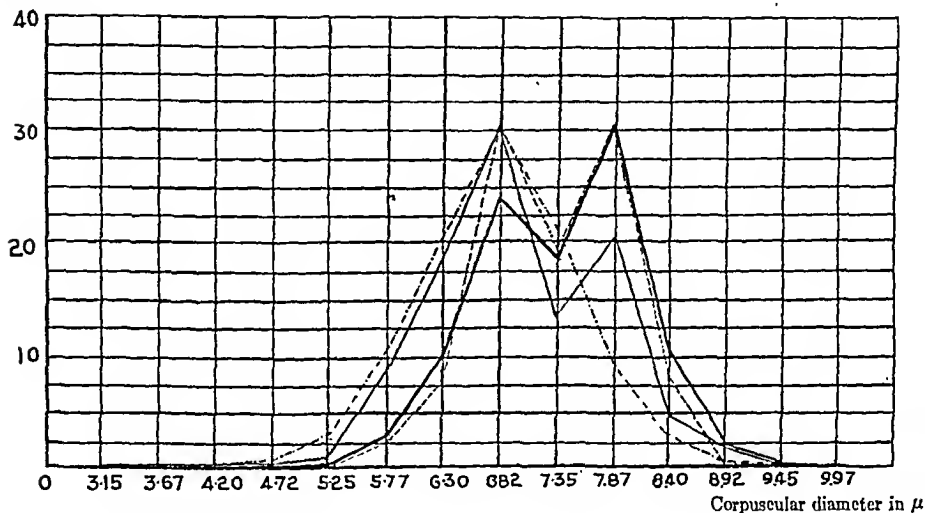
In any case, the approach toward normal of the diameters of the newly formed corpuscles appeared very soon after splenectomy. The approach toward normal of the osmotic resistance, on the other hand, seemed to make its appearance more slowly and was not complete even 7 months after the operation. Thus at the end of this period we were not able to speak of normal erythropoiesis in

all its aspects, but only from the point of view of the erythrocytic diameters.

In the second case the postoperative behavior was somewhat different from that of the first. In short, though there was a rapid disappearance of the icterus with increase in strength and coincident feeling of well-being and a decrease of the anemia (resulting finally in a hyperglobulia, even though of slight degree), the return of the curves of diameters and osmotic resistance to normal was not observed.

CHART 3.—CURVES OF ERYTHROCYTE DIAMETERS. CASE 2.

% of Cells



		D	ψ	σ	I
.....	2. V.34	5,77	6,80	0,79	-0,2
————	13. VI.34	5,77	7,01	0,82	+0,2
—————	25. VI.34	5,25	7,36	0,74	+0,06
-----	12. XII.34	6,82	7,29	0,72	+0,2

Dates.	Hb.	R.B.C., mill. per c.mm.	Color index.	Corpuscular volume, cubic micra.
May 2	52	3.20	0.81	86
June 13	70	3.58	0.98	
25	78	4.40	0.88	
Dec. 12	95	5.56	0.85	

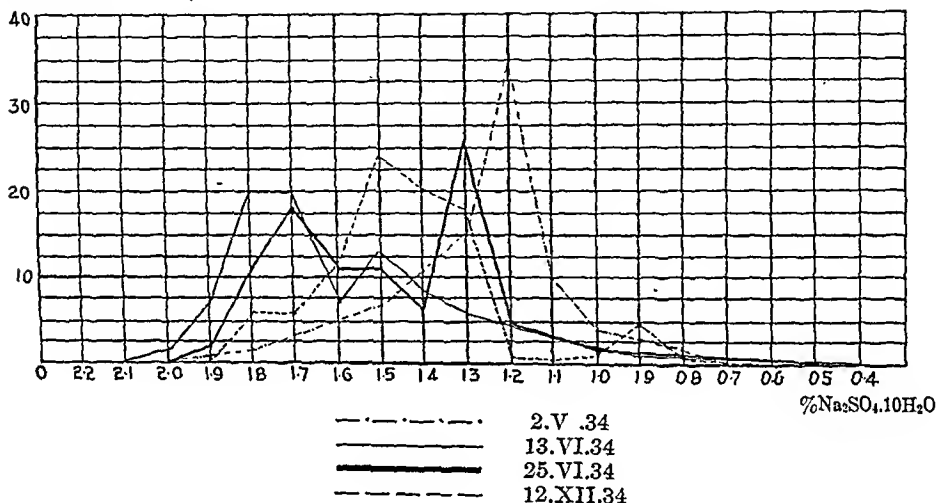
Splenectomy, June 6, 1934.

The curve of red cell diameters (Chart 3) in the period before the splenectomy was monoapical, with a microcytic apex, and exhibited an increased extent of variation. A notable decreased mean diameter, an increased standard deviation (σ) and a negative index of asymmetry. The hyperchromic microcytes made up more than one-half of the globular mass.

The curve of osmotic resistance (Chart 4) was monoapical, with the peak (amounting to about 35% hemolysis with 1.2% of sodium

sulphate) in a position that was almost normal. The minimal resistance, however, was notably diminished and the extent of variations of the curve was, therefore, not greatly increased. The corpuscular population, considered from the point of view of osmotic resistance, thus appeared in a large proportion to be fairly near normal.

CHART 4.—CURVES OF OSMOTIC RESISTANCE OF ERYTHROCYTES. CASE 2.
% Hemolysis



After splenectomy there appeared in the curve of red cell diameters a small normocytic apex beside the microcytic apex; but in the curve of hemolysis the extent of variations was increased through the appearance of a new class of cells with a lower resistance, and all the percentages of hemolysis in the left-hand part of the curve were thereby notably increased. Thus it followed that, while the curve of red cell diameters showed improvement as represented by the heightening of the normocytic peak, which became higher than the microcytic peak, and by the marked diminution in the number of the spheroidal microcytes, while the percentage of reticulocytes and the figures for the curve of reticulocyte diameters returned to normal limit, the curve of osmotic resistance continued to exhibit an abnormal behavior, in that it appeared biapical (the 2 apices appeared, respectively, at the concentration of 1.7% and 1.3% of sodium sulphate).

This abnormal behavior of the resistance of the erythrocytes corresponds closely to the behavior of a case in which at the last blood examination, made about 6 months after splenectomy, the curve of red cell diameters continued to be biapical but with a worse picture than in the preceding examination. This was due to the fact that the microcytic peak had now become of the same height

as the normocytic peak, with an increase in percentages of the spheroidal microcytes. Also in the curve of hemolysis the abnormal position of the principal peak persisted, being localized in the concentration of 1.5% of sodium sulphate; in other words, in proximity to the minimal resistance of a curve of normal hemolysis. The change for the worse of some of the hematologic data in this case can probably be related to the reactivation of a hyperhemolysis in the organs of the reticulo-endothelial system accessory to the spleen.

Thus the picture presented after splenectomy is characterized by biapicality of the curves of red cell diameters and of their osmotic resistance. In the case that was apparently cured there was observed the rapid appearance of a normocytic population in addition to the microcytic cells of lowered resistance. The normocytic population made its immediate appearance with normal diameters; while the curve of the values for osmotic resistance immediately became biapical, a change which denoted the division of the population into two distinct groups of different characters. In this curve the return of a peak in normal or almost normal position was delayed for several months after operation. We then found that both the curve of red cell diameters and the curve of osmotic resistance became monoapical again through the superposition of a normal population on the remnants of the preëxisting pathologic population. More interesting was the fact that the presence of the two peaks in the curves of red cell diameters and resistance was also found in the case which acquired a clinical but not a biologic cure. In this case the biapicality of the curve of red cell diameters never disappeared to give way to a monoapical condition with the peak in normal position. The biapicality of the curve of resistance had a distinctly different form from that of the case that went on to cure.

Conclusion.—The interest in these observations consists in the demonstration of the existence of an approximate cure hematologically, as represented by the appearance of a persistent normocytic reaction of the marrow, even in those cases of hemolytic icterus which do not seem to have been completely cured after splenectomy, as evidenced by the persistence of microcytosis and of erythrocytic fragility, even though slight. We emphasize that the very rapid stabilization of the biapicality of the curves of red cell diameters and osmotic resistance after splenectomy documents in the clearest manner the capacity of the bone marrow to produce normal cells, at least from the point of view of their diameters. This observation is not favorable to the hypothesis that the spheroidal microcytosis represents a constitutional defect of erythropoiesis. In our opinion, it is evidence in favor of the view that, with the cessation of hyperhemolysis, that state of affairs disappears which transforms into an actuality the potential disposition of the bone marrow to form pathologic erythrocytes.

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BIOPSY OF THE STERNAL BONE MARROW.

ITS VALUE IN THE STUDY OF DISEASES OF BLOOD-FORMING ORGANS.

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WITH constantly increasing knowledge in the field of hematology, it becomes more and more evident that the blood picture is not always an accurate reflection of the underlying abnormalities in the

blood-forming organs. The cells in the circulating blood are derived from the bone marrow, the lymphoid tissues and the reticulo-endothelial system. The number of the cells and their differential relationship to each other depend not only upon the phenomena of growth and destruction, but upon important factors governing their release from the hematopoietic centers. Particularly is this true in the case of the bone marrow. The peripheral blood may show all the features suggesting a hypoplastic condition of the bone marrow (anemia, leukopenia, thrombocytopenia), and yet the marrow itself may be intensely hyperplastic. This is the case in both pernicious anemia and primary hypochromic anemia.¹ The condition of the marrow may be identical in 2 cases of myelosis, although the peripheral leukocyte count in 1 may be 200,000, in the other 2000 per c.mm. The most marked leukopenic conditions may be associated with a "pyoid" marrow ("maturation arrest").²

It has, furthermore, become evident that the same blood picture may be brought about by a number of diverse pathologic conditions. Thus: anemia, leukopenia and thrombocytopenia may be associated not only with aplastic and hypoplastic anemia, but with pernicious anemia, primary hypochromic anemia, the various aleukemic leukoses, Hodgkin's disease, lymphosarcoma invading the marrow, metastatic carcinoma, Gaucher's disease and possibly Banti's disease. It is true that certain clues in either the clinical laboratory or hematologic findings usually permit an accurate diagnosis, but an occasional case presents itself in which all efforts at exact diagnosis are at an *impasse*. It is here that the value of the bone-marrow biopsy as a diagnostic procedure has become increasingly important.

Besides its obvious importance in clinical diagnosis, biopsy has been found of great value in the study of the various "blood" diseases. By focussing attention on this all too poorly studied tissue, it has made the pathologist conscious of the unusually interesting histologic pictures which may be present, most reliance in the past having been placed on the gross appearance of the marrow. Special studies of the bone marrow in various diseases are being made and rapidly adding to the extent of our knowledge of the once mysterious "blood diseases."

Methods and Material. The first clinical marrow biopsies were performed, in 1908, by Ghedini.³ Wolff,⁴ in 1903, had already utilized the biopsy in experimental animals and pointed out that the method might be of clinical value. Ghedini,³ Spuler and Schittenhelm,⁵ in 1913, Zadek,⁶ in 1921, Morris and Falconer,⁷ in 1922, all used the tibial marrow, which is not only difficult of approach but often gives negative results. Impetus was given these studies by Seyfarth,⁸ in 1923, when he introduced puncture of the sternum. This bone is easily accessible, its anterior lamella is only 5 mm. in thickness, and it can readily be punctured by a small hand trephine. Weiner and Kaznelson,⁹ in 1926, extended Seyfarth's few observations, and in the same year Escudero and Varela¹⁰ gave their first reports indicating

the diagnostic value of the sternal bone-marrow biopsy. The results of their 9 papers are reviewed in their report of 1932.²³ Peabody,¹¹ in 1926, was still utilizing the tibia in his studies of the bone marrow in pernicious anemia, but since then all the reported studies have been made on the sternum. Arinkin,¹² in 1929, modifying Seyfarth's method by introducing a hollow needle into the sternal marrow cavity and removing some of the liquid or semiliquid marrow, was able to study 180 cases. Arjeff,¹³ in 1931, modified Arinkin's method slightly, and Tuschinsky and Kotlarenko,¹⁴ in 1932, and Tempka and Braun,¹⁵ in the same year, carried on investigations (using Arinkin's technique) of typhoid fever and pernicious anemia. Isaacs,¹⁶ in 1930, studied the "physiologic histology" of the sternal bone marrow and Pokrowsky¹⁷ correlated the state of the reticulocytes in the marrow, with those in the peripheral blood. Recent reports have been made by Barta¹⁸ (22 cases), Nordensen¹⁹ (170 cases with Arinkin's technique), Kossirsky,²⁰ Spartaco,²¹ and Custer.²²

Most of the investigations have been carried out with the semiliquid material obtained either with a hollow needle or by curette following the use of Seyfarth's trephine. Smears of this material have been studied as with the blood. Custer,^{22,24} who has reported systematic observations of the bone marrow both from postmortem and biopsy studies, emphasizes the value of the study of properly fixed sections. In the present investigation,

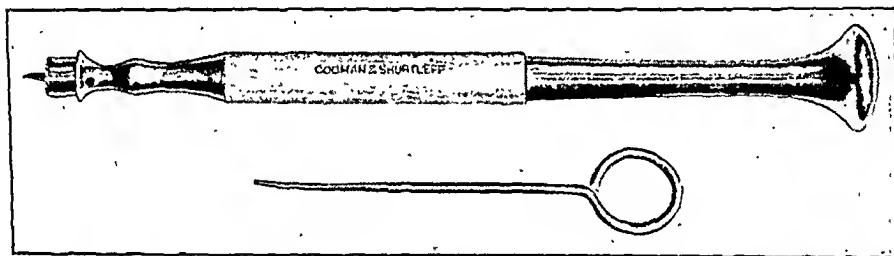


Fig. 1.—The bone marrow trephine (slightly less than actual size), and stilet for extraction of the plug of bone from the "crown."

Seyfarth's technique has been utilized, both smears and sections being prepared. About 125 biopsies have been performed in miscellaneous hematologic conditions. Seyfarth's trephine, slightly modified, was made for us by Codman and Shurtleff, of Boston (Fig. 1). It is essentially a small, steel hand trephine such as is used in trephining the cranium of cats and dogs, the essential feature being a saw-toothed crown, 5 mm. in diameter and 5 mm. long to the bevelled edge. A central protruding cutting edge is present, and small holes at the base of the crown allow entrance of a stilet for the purpose of extracting the bone which is contained after biopsy. I have added a handle at the top of the instrument, to allow a better grasp and more sustained pressure. The sternum is used on account of its accessibility and thin anterior lamella. The procedure is done under aseptic precautions, rubber gloves and sterile gowns being worn. Novocain, 1%, is used as a local anesthetic, the skin over the midsternum in the region of the third or fourth intercostal spaces being infiltrated. A 2- to 4-cm. incision is made directly in the midline, the edges of the wound being retracted with Allis forceps. The periosteum, after being infiltrated with novocain, is incised and retracted by the use of a small periosteal elevator. The bone-marrow trephine is now placed directly over the bare surface of the bone, slight pressure is made, and with a rotating motion from side to side, the marrow cavity is entered. At the moment of entrance, a

"give" is felt, as when entering the spinal canal. With a slight rocking motion, the trephine is removed together with its enclosed plug of bone. The resultant cavity is carefully scooped out by means of a fine curette, such as is used in ophthalmologic surgery, and the soft marrow thus obtained is spread out as with blood smears on sterile glass slides. Touch or imprint preparations are also made either from the plug of bone in the trephine or from small bits of bone removed by curette. These are very gently smeared on glass slides. The wound is closed with one deep silk-worm-gut suture and 2 to 4 horse-hair skin sutures.

Two types of bone-marrow preparations are obtained by this method: sections and smears. The small plug of sternal bone (5 mm. in diameter by 5 mm. in length) is immediately placed into 100 cc. of Zenker's fixative solution containing 5 cc. of glacial acetic acid. After 48 hours, there is usually sufficient decalcification so that microscopic sections can be cut. In rare instances, nitric acid must be used for decalcification. The sections are then run through as in routine pathologic work, and stained with eosin methylene blue. Hematoxylin and eosin may be used, but this staining combination does not give as clear cellular detail. The sections are invaluable for a general picture of the bone-marrow relations, and for the proper understanding of normal or abnormal islands of hematopoietic cells. However, for exact cytologic study the marrow smears cannot be excelled. Wright's stain, diluted half and half with absolute methyl alcohol is used, the stain being allowed to remain for 2 minutes before water is added, the mixture of stain and water remaining for 4 to 8 minutes. Giemsa's stain followed by clearing in xylol, has lately been found much more satisfactory. Differential counts of the marrow smears and sections are made, the smears usually being far more satisfactory for this procedure. The following cell types are set down:

Nucleated red blood cells	{	Normoblasts.	}	in pernicious anemia.
		Erythroblasts.		
		Pro-erythroblasts.		
		Megaloblasts		
		Promegaloblasts		
White blood cells	{	Erythrogones		
		Mature neutrophils.		
		Metamyelocytes.		
		Myelocytes.		
		Pre-myelocytes.		
		Myeloblasts.		
Megakaryocytes.	{	Eosinophils.		
		Histiocytes.		

Differentiation of the various cell types is not a simple matter and can only be mastered by long practice. It is probably best to begin by the careful cytologic study of the peripheral blood from cases of chronic myelosis (myelogenous leukemia).

The white blood cells are tabulated under the respective headings as noted above. These are counted in successive oil-immersion fields, each type of cell being searched for, and its number being recorded. The nucleated red blood cells in the same fields are also recorded. The ratio of nucleated red blood cells to white blood cells is obtained after a suitable number (200 to 500) of white blood cells are counted, and the differential percentages of each type of white blood cell are calculated.

The Normal Marrow. The most careful studies of the normal marrow have been made by Custer,^{22,24} who compared the marrow from the various bones at different ages. He found that the

marrow from different bones varied in cellularity; that the sternum under normal conditions always contained cellular marrow and was most suitable for biopsy study, but that marrow from the vertebrae was the most highly cellular, the more constant in cellular composition and more suitable for postmortem study. In the present study, no biopsy specimens were obtained from entirely normal subjects,* so that standards for normality were necessarily derived from the study of postmortem material. The bone marrow was routinely examined from a large number of autopsies. Usually marrow was obtained from one of the ribs by expressing some of the soft material from a cut end. This made decalcification in nitric acid unnecessary. Fixation was made in Zenker's solution, paraffin sections being run through in the ordinary way and stained with eosin methylene blue. The best specimens were those obtained within a few hours after death. Specimens obtained 12 hours or more after death were often difficult to study for cellular detail. Unless autopsy was performed within an hour or two after death, the sections were usually decidedly inferior to those obtained at biopsy. Bone-marrow smears from autopsy specimens were ordinarily of little value.

It is almost impossible to obtain a normal marrow from an autopsy specimen, since death, unless accidental, is due to some definite cause and is frequently associated with a terminal infection. However, since the gross abnormalities, due to such "blood" diseases as leukemia and pernicious anemia, are usually absent, it is possible to obtain from the study of a large number of specimens a fairly accurate idea as to the relative percentages of various cells and the ratio of the nucleated red blood cells to white blood cells.

Results. From a study of about 200 bone-marrow sections obtained at autopsy, it is possible to present the following figures as representing the approximate cellular constituents found in the normal (rib) marrow:

Ratio of nucleated red blood cells to white blood cells: approximately 1 to 1 (variation from 0.6 to 1 to 1.2 to 1).

DIFFERENTIAL COUNT OF THE WHITE BLOOD CELLS:

Mature neutrophils, 2 to 5%.	Pre-myelocytes and myeloblasts, 1 to 5%.
Metamyelocytes, 20 to 40%.	Eosinophils, 1 to 5%.
Myelocytes, 30 to 50%.	Histiocytes, 1 to 2%.

DIFFERENTIAL COUNT OF THE RED BLOOD CELLS:

Normoblasts, 80%.	Erythroblasts, 20%.
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The megakaryocytes are sprinkled throughout the section, 2 to 10 usually being seen in counting 300 white blood cells (0.7 to 3.3%).

* Bone marrow which appeared to be entirely normal was obtained from a few patients with malignant hypertension.

A. Complications. Biopsies were done in a variety of hematologic conditions, ranging from severe anemia to polycythemia and from agranulocytosis to leukemia, as well as in cases presenting marked reduction in blood platelets. Two slight complications were encountered. In a case of diffuse acute lupus erythematosus, the skin wound failed to heal properly; in a case of chronic myelosis, a moderate degree of hemorrhage took place when the skin sutures were removed. Oozing at the time of operation in cases associated with marked reduction in blood platelets was always controlled by pressure. In no case was it necessary to use bone wax, although its use was considered in one or two instances.

B. Classification of Cases and Description of Bone-marrow Findings. The following is a classification of the diseases in which biopsy was done:

Pernicious anemia.	Reticulosis (monocytic leukemia).
"Primary" hypochromic anemia.	Acute leukemic.
Secondary hypochromic anemia.	Chronic aleukemic.
Congenital hemolytic anemia.	Agranulocytosis.
Aplastic anemia.	Polycythemia vera.
Hypoplastic anemia.	Purpura hæmorrhagica.
Myelosis (myelogenous leukemia).	Hodgkin's disease.
Chronic leukemic.	Lymphosarcoma metastasized to marrow.
Chronic aleukemic.	Banti's disease.
Acute leukemic.	Lupus erythematosus acuta.
Acute aleukemic.	Enterogenous cyanosis.
Lymphadenosis (lymphatic leukemia).	Chronic nephritis.
Chronic leukemic.	Malignant hypertension.
Chronic aleukemic.	Hemochromatosis.
? Chronic leukemic.	

Since this paper deals chiefly with the diagnostic value of the bone-marrow biopsy, no detailed descriptions of the findings at biopsy in the various conditions classified above will be given. However, a few general remarks (limited to what was actually found at biopsy) will be made about each condition in which a biopsy was done.

Pernicious Anemia. Fourteen biopsies were performed. In 5 cases, biopsies both before and after treatment were made. In relapse, the marrow is characteristic: hyperplastic, without fat cells, and presenting large numbers of large embryonic nucleated red blood cells (promegaloblasts and megaloblasts). These are often present in "islands" and mitotic figures are numerous. Numerous cells resembling small lymphocytes, which have been called "crythrogoncs" are seen. Histiocytes are increased in number and apparent transitions between these embryonic cells and the promegaloblasts can be seen (Fig. 2). The percentage of normal nucleated red blood cells is

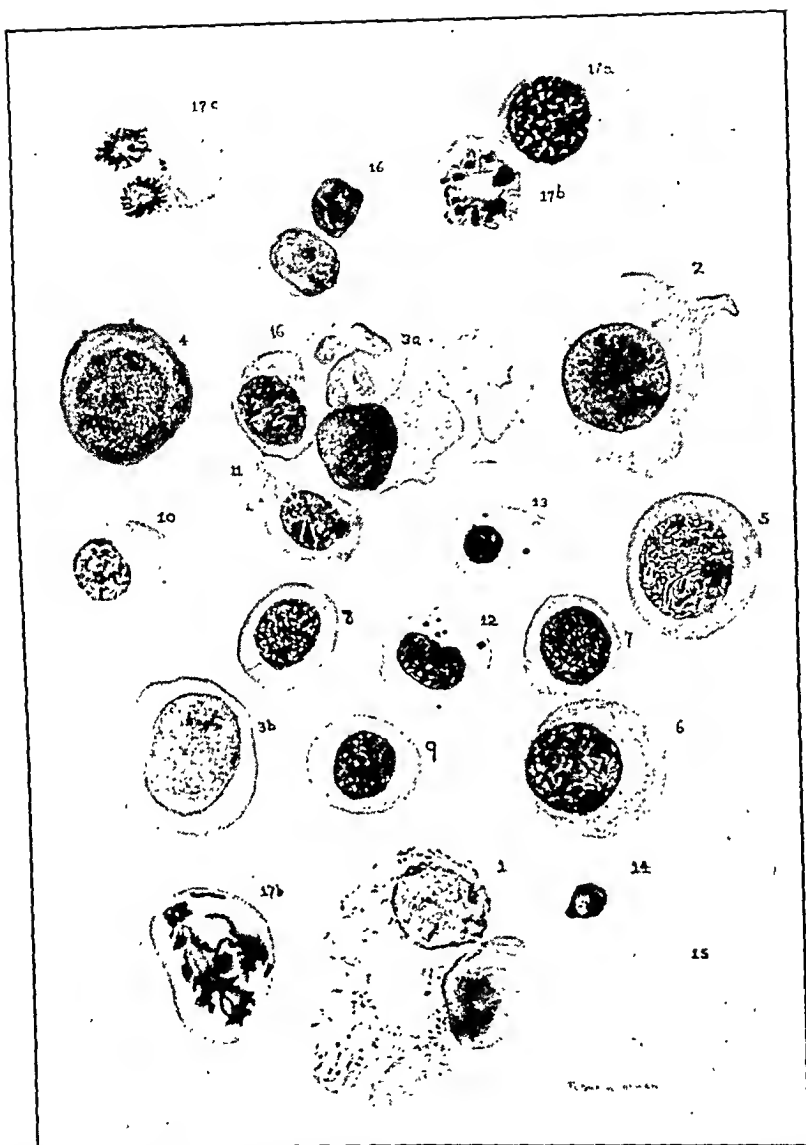


FIG. 2.—Photograph of water-color paintings of red blood cells observed at sternal bone-marrow biopsy in a case of pernicious anemia in relapse. The cells, numbered 1 to 15, inclusive, illustrate what appear to be transitions in the development of the red blood cell of pernicious anemia from the histiocyte to the mature macrocyte. 1, Typical histiocyte (hemohistioblast); 2, 3a and 3b, early promegaloblasts (these cells retain many of the features of leukocytes); 4, 5 and 6, promegaloblasts; 7 and 8, megaloblasts; 9 and 10, proerythroblasts; 11, 12 and 13, erythroblasts; 14, normoblast; 15, erythrocyte (macrocyte); 16, "erythrogonos" (lymphoid-looking cells found in pernicious anemia); 17a, 17b, 17c, 17d, megaloblastic cells in various types of mitosis.



FIG. 3.—Photomicrograph of section of sternal bone marrow removed at biopsy in Case M. C. (Table 1). Aleukemic myelosis. ($\times 985$.) Note the large number of proliferating myeloblasts with prominent nucleoli (*Myb*), the few myelocytes (*Mye*), and the marked reduction in nucleated red blood cells (*Ery*).

FIG. 4.—Photomicrograph of section of sternal bone marrow in Case M. G. (Table 3). Lymphosarcoma of spleen metastasizing to bone marrow. Smears show no marrow cells. Sections show replacement of normal marrow tissue by loose fibrous tissue. ($\times 985$.)

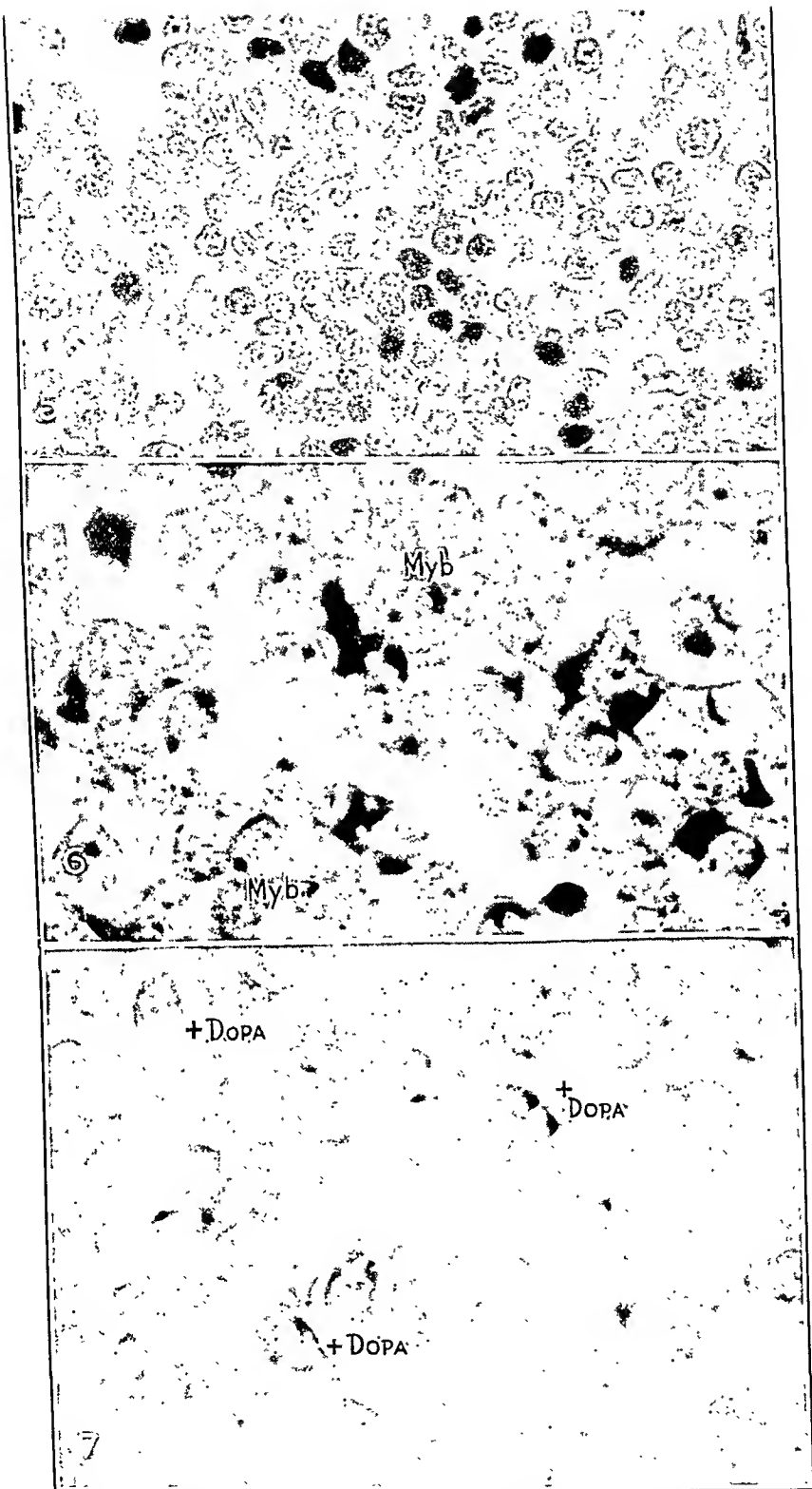


FIG. 5.—Photomicrograph of section of spleen removed at operation in Case M. G. (Table 3). Complete replacement of splenic architecture by rapidly proliferating primitive cells; lymphoblasts. ($\times 700$.)

FIG. 6.—Photomicrograph of section of sternal bone marrow in Case F. L. (Table 4). Myelosarcoma (chloroma) with terminal aleukemic myelosis. ($\times 985$.) Stuffing of marrow cavity with proliferating myeloblasts (*Myb*). Rare erythroblastic cell or megakaryocyte.

FIG. 7.—Photomicrograph of section of tumor of uterus removed at operation in Case F. L. (Table 4). Myelosarcoma of uterus. ($\times 985$.) Dopa stain. Note the neoplastic process composed of embryonic cells (myeloblasts), many of them showing a positive "dopa" reaction.

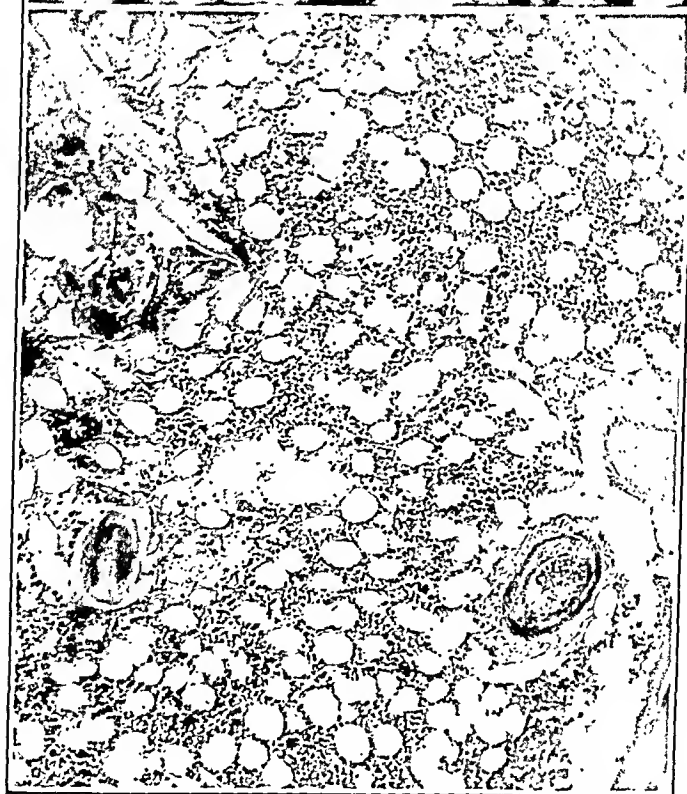
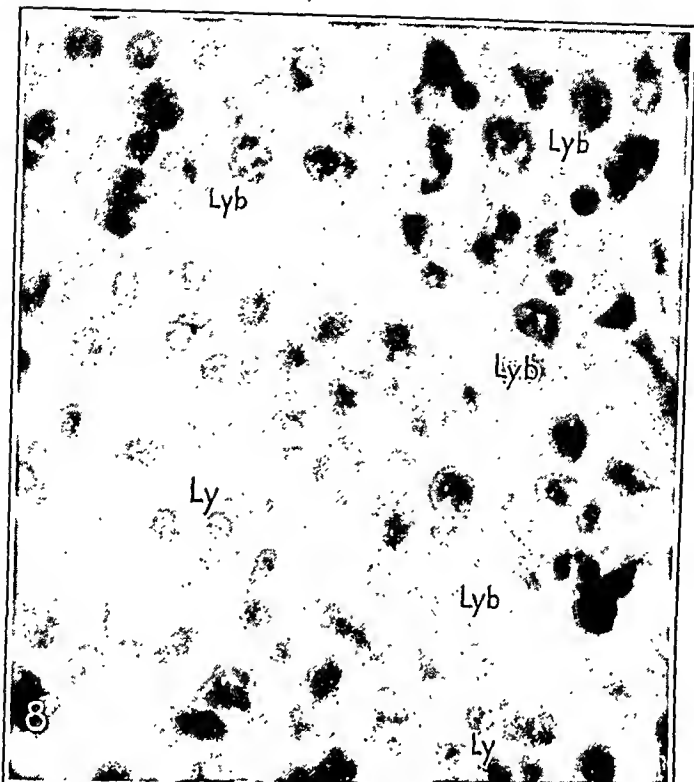


FIG. 8.—Photomicrograph of section of bone marrow in Case M. Z. (Table 5). Sub-acute aleukemic lymphadenosis. ($\times 985$.) Note the large number of lymphoblasts (*Lyb*) and lymphocytes (*Ly*) infiltrating the marrow tissue.

FIG. 9.—Photomicrograph of section of bone marrow in Case Ellen O'C. (Table 6). Hypoplastic anemia; arteriosclerosis. ($\times 70$.) Note the marked increase in number of fat cells (sternal marrow). At the right is seen an arteriole showing evidences of sclerosis.

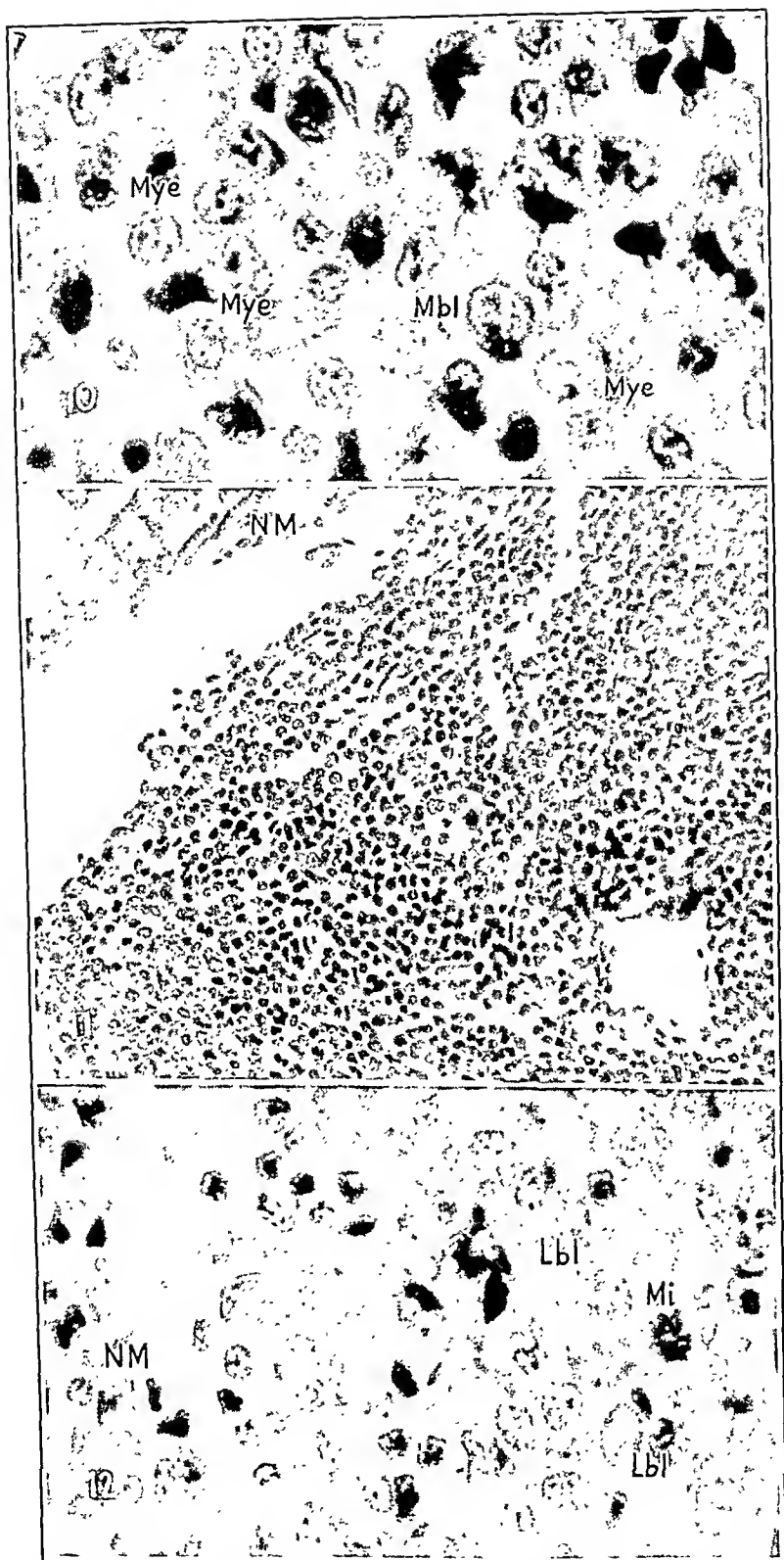


FIG. 10.—Photomicrograph of section of bone marrow in Case R. R. (Table 7) Aleukemic myelosis. ($\times 985$.) Note the crowding of the marrow with granulocytic cells, myeloblasts (*Mbl*) and myelocytes (*Mye*), myelocytes predominating.

Figs. 11 and 12.—Photomicrographs of section of bone marrow in Case E. S. (Table 8). Lymphosarcoma metastasizing to bone marrow. Fig. 11, low power ($\times 300$) and Fig. 12, high power ($\times 1000$). Note the mass of proliferating cells infiltrating and invading the normal marrow tissue (*NM*). The proliferating cells are identified as lymphoblasts (*Lbl*). A mitotic figure (*Mi*) is seen.

markedly diminished, their number varying with the degree of relapse. In severe relapse, only a few erythroblasts and normoblasts are seen. After the institution of liver treatment, the marrow resumes to great extent its normal appearance; normoblasts are now the predominating cell and only a rare megaloblast is seen. The white blood cells now become present in normal numbers, together with great diminution in the histiocytes and the "erythrogonos."

Secondary Hypochromic Anemia. Of 3 cases studied, in 2 the anemia was associated with hypernephroma and the marrow showed hypoplasia of the erythroblastic tissue; in the other, with chronic hemorrhage the red cell-forming tissue was hyperplastic.

Primary Hypochromic Anemia. Kaznelson, Reimann and Weiner,²⁵ and I¹ have described the bone-marrow findings in this disease. The disease may be idiopathic in nature or may be associated with diverse etiologic factors leading to a chronic iron deficiency state. Clinically there is anemia of low color index and of small red cells associated with achlorhydria. The bone marrow, despite the often striking anemia, is hyperplastic. There is great increase in the normal nucleated red cells (erythroblasts and normoblasts), megaloblasts not being found. I have likened the bone-marrow findings in this disease with those found in pernicious anemia.¹ The bone marrow in both conditions is, despite the anemia, hyperplastic, the red cells apparently being unable to mature properly unless the appropriate medication (liver extract in the one case, large doses of iron in the other) is given. Crowding of the marrow by increased formation of nucleated red blood cells results in some diminution in both the white blood cells and megakaryocytes.

Congenital Hemolytic Anemia. The bone marrow has been but little studied in this disease. Biopsies were done in 2 cases: in 1, the ratio of red blood cells to white blood cells was 0.4 to 1, and the percentage of erythroblasts was greatly increased (80%); in the other, the ratio of red blood cells to white blood cells was about 1 to 1, and here, too, there was a marked relative increase in erythroblasts (to 80%). In this case there was a definite increase in histiocytes, although no cells with phagocytosed inclusions could be seen.

Aplastic Anemia. Of 5 cases studied, in 4 severe cases the marrow was almost entirely converted to fat, only a few cells being present. In a fourth, due apparently to repeated "courses" or arsphenamin, there was almost complete absence of nucleated red blood cells (ratio of red to white blood cells, 0.075 to 1); although white blood cells were present in fairly large numbers. After several transfusions, this patient finally recovered completely.

Mycosis. In 10 cases studied, the findings varied directly with the type of the disease—whether acute or chronic. In the chronic type—leukemic or aleukemic—there was marked increase in leuko-

cytes, the ratio of red blood cells to white blood cells varying from 0.05 to 1 to 0.7 to 1. Differential count of the white cells was distinguished by a marked increase (often up to 40 to 50%) in myeloblasts, myelocytes, however, being present in almost normal numbers. The normal growth of red blood cells and usually of megakaryocytes is interfered with by the large numbers of proliferating white blood cells, although in one case large numbers of megakaryocytes were found. In the acute cases the marrow was overrun by large numbers of myeloblasts, frequently in mitosis, myelocytes and more mature neutrophils being but rarely seen. In this mass of cells there is almost complete disappearance of nucleated red cells and megakaryocytes. In 2 subacute cases the findings were intermediate between those of chronic and acute leukemia. Whether the white blood cell count was high or low (leukemic or aleukemic leukemia), the cellular picture in the bone marrow was found to be identical.

Lymphadenosis (Lymphatic Leukemia). The bone marrow in 6 cases of the chronic variety of this disease showed varying degrees of invasion with lymphocytes, with variable distortion of and interference with normal cell growth. In 1 case in which the diagnosis of early chronic lymphatic leukemia was suspected, because of long-standing absolute lymphocytosis (white blood cells, 15,000; lymphocytes, 70 to 80%), the marrow showed the presence of more lymphocytes than of ordinary bone-marrow white cells. There appeared, however, to be little interference with red blood cell growth.

Reticulosis (Monocytic Leukemia). I²⁶ have described the bone marrow findings in this third type of leukemia, which is distinguished hematologically by marked increase in monocytes and histiocytes. The acute type exhibits overwhelming proliferation of histiocytes, only a small amount of reticulum being present. In an example of the chronic aleukemic type which was studied, there was marked increase in reticulum with the presence of numerous giant cells.

Agranulocytosis. In 1 patient studied there was complete absence of mature neutrophils, metamyelocytes and myelocytes, the only remaining leukocytes being a few myeloblasts.

Polycythemia Vera. The bone marrow was studied in 4 patients with this condition, in whom the red blood cell count ranged between 7,000,000 and 9,000,000. In each case there was marked hyperplasia of both red and white blood cell forming elements, the ratio remaining normal (1 to 1). Fat cells were conspicuously diminished. Occasional islands of primitive nucleated red blood cells could be seen. The megakaryocytes were conspicuously increased in number. The bone marrow thus showed a generalized proliferation of its three elements: erythroblasts, myeloblasts and megakaryocytes.

Secondary Polycythemia. The polycythemia in this case (K.) was secondary to chronic cardiac and pulmonary disease. Approximately the same findings as were present in the "true" type of polycythemia were observed.

Purpura Hemorrhagica. In 1 chronic case in which the blood platelet count was 40,000 per c.mm., the bone marrow disclosed nothing remarkable. Megakaryocytes were present in normal number, although they appeared smaller than normal. This patient had a long remission after splenectomy, but is now again in relapse.

Hodgkin's Disease. Recent papers have directed attention to the generalized character of the lesions in Hodgkin's disease. In a recent paper I²⁶ have discussed the cell type involved and have presented reasons for assuming that it is of the reticulum cell (histiocyte) series. In 6 cases of Hodgkin's disease studied at biopsy, the leukopoietic elements in the bone marrow were markedly hyperplastic, the ratio of white to red blood cells being conspicuously increased. In each case there was marked increase in immature leukocytes. Thus, in case C. G., there were 12% myeloblasts and pre-myelocytes, in case A. M. these cells numbered 24.6% of the total leukocytes, and in case E. B., 36.2% of these cells were present. The histiocytes were increased only slightly in case C. G. and E. B. (2.8% and 2%, respectively), but were markedly increased in case A. M. to 24%. In the latter case the disease appeared to be more generalized than in the other two and was associated with marked anemia, leukopenia and splenomegaly. The megakaryocytes in this case were also greatly increased, as many as 7 being found in one oil-immersion field. These giant cells were normal in the remaining cases.

Lymphosarcoma With Metastasis to Bone Marrow. This is a rare lesion, although I have observed it in 5 cases. In 3 cases in which biopsy was done, the bone marrow showed almost complete absence of normal marrow tissue, with large numbers of lymphoblasts and a few lymphocytes.

Banti's Disease. The great majority of cases diagnosed as Banti's disease which I have seen have been found on more careful study to be some other disease, usually chronic aleukemic myelosis. In 1 case (S. W.) studied with bone-marrow biopsy, however, the diagnosis at present appears to be that of Banti's disease rather than that of aleukemic myelosis, as originally considered. In this case there was clinically several attacks of hematemesis, marked splenomegaly, leukopenia, thrombocytopenia and moderate anemia. Bone-marrow biopsy showed increase in white blood cell-forming elements, with increase in embryonic white blood cells (myeloblasts and pre-myelocytes) to 44%. The diagnosis in this patient is still in doubt, although Banti's disease appears to be at present the most probable.

Acute Lupus Erythematosus. The acute or disseminated form of lupus erythematosus appears to be a general disease rather than one limited to the skin. In 1 case in which biopsy was done there was, besides the skin lesions, splenomegaly, generalized lymph-node enlargement, leukopenia, thrombocytopenia and moderate anemia. The bone marrow disclosed a definitely hyperplastic marrow with small areas of necrosis affecting particularly the leukopoietic elements. There was an increase in reticulum cells throughout the section.

Enterogenous Cyanosis. In this highly unusual case there was clinically a slate-gray-blue color of the skin and mucous membranes, moderate hypochromic anemia and diarrhea, apparently due to pinpoint ulcerations in the rectum. There was a varying percentage of "inactive" hemoglobin, the oxygen-carrying hemoglobin (as determined by the Van Slyke-Neill oxygen capacity method) being much less than the total hemoglobin (as determined by the Wong iron method or the cyanhemoglobin method of Stadie). Spectrophotometric studies showed at times methemoglobin, at times sulphhemoglobin, at times both. The bone marrow showed hypoplasia of the red cell-forming elements, the ratio of nucleated red to white blood cells being 0.34 to 1. There was definite increase in histiocytes to 10%.

Chronic Nephritis. In 4 cases of chronic nephritis associated with more or less marked nitrogen retention and moderate to marked anemia, the biopsy in each case showed distinct hypoplasia of erythropoietic tissue, neither the leukopoietic elements nor megakaryocytes being affected.

C. The Use of the Bone-marrow Biopsy in Clinical Practice. At the beginning of this study, the bone-marrow biopsy was resorted to in almost every hematological case whether or not a diagnostic problem presented itself. In this way standards of comparison were obtained, together with actual information which had heretofore not been well documented. In the past 2 years, however, the biopsy has been chiefly utilized when diagnosis was actually in doubt and when it seemed probable that it could be settled by this test. Of the approximately 125 cases in which biopsy was done, the exact hematologic diagnosis remained in doubt in 26, even after careful clinical, laboratory and hematologic studies had been made. Of this group of 26, the diagnosis was definitely established at biopsy in 20; in 6, the diagnosis still remained in doubt even after biopsy. A short résumé of 18 cases in which diagnosis was difficult will be given, together with the findings at biopsy, only positive findings being reported. The following abbreviations will be used: R.B.C. (red blood cell count), W.B.C. (white blood cell count), N. (neutrophils), L. (lymphocytes), M. (monocytes).

Case Abstracts. 1. M. C. Seen with Dr. R. B. Buck at New England Baptist Hospital. *Pre-biopsy diagnosis:* unexplained anemia; ? agranulocytosis. *Biopsy diagnosis:* acute aleukemic myelosis (Table 1).

TABLE 1.—(CASE M. C.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<p><i>History:</i> female, aged 45. Weakness since July, 1928. September, 1928, pain in region of anus together with marked swelling. October 15, 1928, hemorrhoidectomy followed by increasing weakness and pallor.</p> <p><i>Examination:</i> necrotic ulceration of rectum, marked pallor.</p>	<p>Hemoglobin, 60 to 17%. R.B.C., 3.2 to 1.08. W.B.C., 4000 to 1700. Platelets, 100,000. Red blood cells: achromia +, anisocytosis ++, poikilocytosis ++. Differential count: P., 4; L., 80%; M., 16%.</p>

Final Clinical Diagnosis.

Agranulocytosis.

Unexplained anemia. (Previous diagnoses: typhoid fever, miliary tuberculosis, etc.)

<i>Bone-marrow Biopsy.</i>	<i>Further Findings.</i>
<p>Many islands of actively proliferating myeloblasts. Conspicuous reduction in erythroblastic cells and in megakaryocytes. (Fig. 3.)</p> <p><i>Diagnosis:</i> acute myelosis.</p>	<p><i>Postmortem:</i> large spleen, with but little change microscopically. Bone marrow showed active hematopoiesis with many megakaryocytes.</p>

Final Diagnosis.

Acute (aleukemic) myelosis.

2. RHODA L. B.I.H. 7287. *Pre-biopsy diagnosis:* chronic unexplained anemia; ? atypical lymphoblastoma; ? aleukemic lymphadenosis. *Biopsy diagnosis:* lymphosarcoma or lymphadenosis with bone-marrow invasion. *Final diagnosis:* chronic aleukemic lymphadenosis.

An American-Jewish girl, aged 4½ years, became nauseated 5 weeks before admission to the hospital, on August 19, 1930. She gradually became listless and pale. On examination she showed rather marked pallor, moderately enlarged cervical lymph nodes and a few small axillary lymph nodes. *Blood studies:* hemoglobin, 29%; R.B.C., 2,110,000; W.B.C., 2100; platelets, 274,000; reticulocytes, 0.4%. Differential count: N., 7%; L., 84%; M., 9%. Several lymphocytes were definitely abnormal and an occasional questionable lymphoblast was seen. *Bone-marrow biopsy* (September 17, 1930): almost complete replacement of the bone marrow by large numbers of lymphoblasts. In counting 1000 lymphoblasts only 3 myelocytes, 2 metamyelocytes, 1 mature neutrophil and 2 normoblasts were seen. *Course:* There was mild fever. The patient was given two transfusions of blood, ferric ammonium citrate and liver extract without appreciable effect. The liver gradually became enlarged. The patient was discharged in essentially the same condition as on entrance. In November, 1930, she began to improve, and there was rise in hemoglobin, erythrocyte and leukocyte counts to almost normal. There was continued improvement for about

6 months, but in March, 1931, she again became weak, listless and pale. At that time there was generalized enlargement of lymph nodes, liver and spleen; the leukocyte count was 12,000 to 15,000 per c.mm., with 80 to 90% lymphocytes. The patient died in April, 1931. Autopsy was not obtained. *Final diagnosis*: chronic lymphatic leukemia (aleukemic); ? lymphosarcoma with metastases to bone marrow.

3. MOSES S. B.I.H. 5144. *Pre-biopsy diagnosis*: splenomegaly, ? type; Banti's disease. Secondary anemia. *First biopsy diagnosis* (January 25, 1930): hypoplastic marrow. *Second biopsy diagnosis* (April 28, 1931): chronic (aleukemic) myelosis.

A Jewish clothing peddler, aged 70, entered the hospital, on January 21, 1930, complaining of pallor, weakness and swelling of the abdomen of about 1 year's duration. Examination disclosed sallow-yellow pallor, ascites and a large thin spleen extending to the crest of the ilium; the liver was not felt. *Blood studies*: hemoglobin, 48%; R.B.C., 2,690,000; W.B.C., 3600; platelets, 140,000; reticulocytes, 3.5%. The red blood cells showed slight achromia, moderate anisocytosis and poikilocytosis. Differential count: N., 56% (8 band forms); L., 31%; M., 7%; E., 6%. *Interpretation of blood picture*: hypoplasia or destruction of bone marrow, ? type. *Bone-marrow biopsy* (January 25, 1930): ratio of nucleated R.B.C. to W.B.C., 1 to 0.64. Differential count of the W.B.C.: mature neutrophils, 7%; metamyelocytes, 26.8%; myelocytes, 30.7%; pre-myelocytes and myeloblasts, 22.2%; eosinophils, 15%. The bone-marrow sections showed nothing remarkable.

The patient was readmitted on April 16, having felt better until January, 1931. There were signs of cardiac decompensation with fluid at both bases, ascites and a large palpable spleen. The blood picture showed no material change from the previous year, *i. e.*, there was anemia, leukopenia and thrombocytopenia, interpreted as signifying a hypoplastic bone marrow, due to (1) ? "splenic anemia" with fibrosis, (2) myelogenous leukemia (aleukemic), (3) neoplastic metastasis to the marrow. A second *bone-marrow biopsy* was done on April 28. Parts of the section showed hyperplasia, the cell type being the myeloblast. Bone-marrow smears showed a ratio of W.B.C. to nucleated R.B.C. of 1.4 to 1, with 18% myeloblasts. *Course*: The cardiac decompensation improved. There was marked reduction in size of the spleen following Roentgen radiation. The patient is still being followed. The blood picture remains essentially the same.

4. EMMA B. Seen with Dr. J. H. Pratt at New England Baptist Hospital. *Pre-biopsy diagnosis*: splenomegaly ? type; ? pernicious anemia. *Biopsy diagnosis*: chronic (aleukemic) myelosis.

A woman, aged 49, complained of increasing weakness, epigastric pain, and loss of weight, beginning in August, 1930. *Examination*, November 29, disclosed marked pallor, a red tongue denuded of coat, and a large spleen extending to the crest of the ilium. *Blood studies*: hemoglobin, 35 to 40%; R.B.C., 1,820,000 to 2,200,000; W.B.C., 1600 to 3400; platelets, 22,000 to 120,000; reticulocytes, 5.5%. Differential count of the W.B.C. showed: mature neutrophils, 46%; metamyelocytes, 18%; myelocytes, 0.8%; L., 22.8%; M., 11.6%. *Interpretation of blood studies*: a "destructive" condition of the bone marrow (anemia, leukopenia, thrombocytopenia), probably leukemic in type. *Bone-marrow biopsy* (November 29, 1930): a hyperplastic marrow with areas of proliferating myeloblasts. Differential count of the bone-marrow leukocytes: mature neutrophils, 2%; metamyelocytes, 19.5%; myelocytes, 19%; pre-myelocytes and myeloblasts, 51%; histiocytes, 4%. *Diagnosis*: chronic aleukemic myelosis. The

patient died on December 7, 1930, following severe hemorrhages from the lungs, throat and nose. Autopsy not obtained.

5. CHARLES M. Seen with Drs. Smart and Robinson, Laconia, N. H.* *Pre-biopsy diagnosis:* chronic unexplained anemia; relapsing fever. *Biopsy diagnosis:* ? generalized Hodgkin's disease. *Final diagnosis:* aleukemic reticulosis (Table 2).

TABLE 2.—(CASE C. M.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<i>History:</i> male, aged 39. Weakness, 5 months. Fever, relapsing in type, 3 months. Pallor, loss of weight, 2 months.	Hemoglobin, 55 to 30%. R.B.C., 2.83 to 1.80. W.B.C., 3500 to 1100. Platelets, 123,000. Reticulocytes, 1.4%.
<i>Examination:</i> pallor: Spleen just felt; One supraclavicular lymph node felt.	Red blood cells: achromia 0; anisocytosis ++; poikilocytosis ++; polychromatophilia +.
<i>Laboratory findings:</i> All negative.	P., 72.5% (8.5 "band forms"); L., 9.5%; M., 16% (histiocytes, 1); E., 1.5%.

Clinical Diagnosis.

"Destructive" process of bone marrow: ? lymphosarcoma; ? Hodgkin's disease. (Previous diagnoses: typhoid fever, malaria, agranulocytosis, etc.)

<i>Bone-marrow Biopsy.</i>	<i>Postmortem Examination.</i>
Dense tissue replacing almost entirely the normal elements; hyperplasia of reticulum cells; giant-cell formation. <i>Diagnosis:</i> ? Hodgkin's disease involving bone marrow.	Proliferation of reticulo-endothelial cells throughout entire body; liver, spleen, lymph nodes, bone marrow, omentum, etc.

Final Diagnosis.

Aleukemic reticulosis (generalized Hodgkin's disease?).

6. MITCHELL G. B.I.H. 3491. *Pre-biopsy diagnosis:* ? Banti's disease; chronic hypoplastic anemia ? type. *First biopsy diagnosis:* hypoplastic bone marrow. *Second biopsy diagnosis:* lymphosarcoma with invasion of bone marrow (Table 3).

7. MARTIN P. Boston Disp. 138552. *Pre-biopsy diagnosis:* pernicious anemia. *Biopsy diagnosis:* ? chronic lymphatic leukemia (aleukemic); ? lymphosarcoma with metastasis to bone marrow.

A man, aged 53, complained of vague pains in the joints, slight weight loss and spontaneously appearing ecchymoses, all of about 6 months' duration. *Examination* showed nothing but moderate pallor. There was no icterus; the tongue was normal; neither the spleen, lymph nodes nor liver were palpable. *Blood:* hemoglobin, 62%; R.B.C., 3,140,000; W.B.C., 4650; platelets, 161,000. Differential count of the white cells: neutrophils, 12%; lymphocytes, 88% (several very large lymphocytes; no lymphoblasts; monocytes, 0. The red cells showed no achromia and many macrocytes; average red blood cell diameter, 7.9 micra. *Other laboratory data:* gastric analysis showed 12 units of free hydrochloric acid after injection of histamin.

* This case has been fully described in a previous paper.²⁶

Icterus index, 6. *Interpretation:* blood picture shows macrocytic anemia, probably pernicious anemia; very high percentage of lymphocytes unusual; presence of free hydrochloric acid in gastric juice makes diagnosis doubtful. *Bone-marrow biopsy:* *Smears:* ratio nucleated red blood cells to white blood cells, 0.02 to 1. Differential count of white blood cells: lymphocytes, 99.2%; granulocytes, 0.8%. *Sections:* fibrous marrow in parts; packing with lymphoblasts and lymphocytes in other portions; several mitoses. Rare normal marrow cell present. *Diagnosis:* ? lymphatic leukemia or lymphosarcoma metastasizing into marrow. *Course:* No improvement with parenteral liver therapy or large doses of iron. The patient escaped from observation.

TABLE 3.—(CASE M. G.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<i>History:</i> male, aged 13. November, 1928, recurring fever, weakness, swelling of joints. March, 1929, splenomegaly noted.	August, 1929: Hemoglobin, 58%. R.B.C., 3.31. W.B.C., 2000. Reticulocytes, 0.6%. Platelets, 60,000.
<i>Examination:</i> Intermittent fever; pallor; moderate splenomegaly.	Red blood cells: achromia +; anisocytosis ++; poikilocytosis ++. Differential: P., 61%; L., 37%; M., 2%.

Clinical Diagnosis.

Subacute bacterial endocarditis; Banti's disease; splenic anemia; ? Hodgkin's disease.

<i>Bone-marrow Biopsy.</i>	<i>Splenectomy.</i>
<i>Bone-marrow biopsy 1:</i> smears showed no marrow cells. Sections showed replacement of normal marrow tissue by loose fibrous tissue (Fig. 4, $\times 985$).	<i>Spleen</i> (Fig. 5, $\times 700$): complete replacement of splenic architecture by rapidly proliferating primitive cells; lymphoblasts.
<i>Diagnosis:</i> fibrosis of marrow.	<i>Diagnosis:</i> primary lymphosarcoma of spleen.
<i>Bone-marrow biopsy 2</i> (after splenectomy): smears showed very few marrow cells. Almost all cells large, with very large nuclei. Oxidase stain negative. Apparent transitions to lymphocytes. Sections showed replacement of marrow by fibrous tissue in midst of which were present large primitive cells.	Autopsy not obtained.
<i>Diagnosis:</i> Fibrosis of marrow secondary to metastasizing lymphosarcoma.	

Final Diagnosis.

Primary lymphosarcoma of spleen, metastasis to bone marrow, "myelophthisic" anemia.

8. SARAH F. Boston Disp. 276903. *Pre-biopsy diagnosis:* chronic aleukemic myelosis. *Biopsy diagnosis:* hypoplastic bone marrow. *Final diagnosis:* hypernephroma of left kidney with metastases.

A woman, aged 53, complained of weakness. *Examination* disclosed slight pallor, a large mass in the left upper quadrant of the abdomen diagnosed as spleen, and a liver edge palpable 3 fingers' breadth below the right costal margin. *Blood*: hemoglobin, 58%; R.B.C., 3,200,000; W.B.C., 5800. Red blood cells: slight achromia, slight anisocytosis and poikilocytosis. White blood cells: N., 82% (8 metamyelocytes); L., 12%; M., 6%. *Interpretation*: large spleen, slight anemia, probably chronic myelogenous leukemia (aleukemic). *Bone-marrow biopsy*: *Smears*: R.B.C. to W.B.C., 1.1 to 1. Leukocytes: mature N., 2.5%; metamyelocytes, 44%; myelocytes, 36%; myeloblasts, 9%; eosinophils, 3.5%. *Sections*: a hypoplastic marrow. *Later studies*: Intravenous urography showed large mass in abdomen to be kidney—confirmed by retrograde pyelography. Chest plates showed metastatic mediastinal shadows. Liver became larger and the patient died, January 30, 1932.

9. GEORGE A. B.I.H. 17396. *Pre-biopsy diagnosis*: ? aleukemic reticulosis (generalized Hodgkin's disease); ? aleukemic myelosis. *Biopsy diagnosis*: myelosis. *Final (postmortem) diagnosis*: generalized Hodgkin's disease (aleukemic reticulosis or aleukemic monocytic leukemia).

A man, aged 29, complained of anorexia, weakness and loss of weight of 10 months' duration and of bouts of fever and severe night sweats of 3 months' standing. *Examination* revealed a temperature of 104° F., extreme pallor, generalized slight lymphadenopathy and a just palpable spleen. *Blood*: hemoglobin, 58%; R.B.C., 3,300,000; W.B.C., 4200; platelets, 170,000; N., 66% (24% metamyelocytes); L., 5%; M., 21% (13% histiocytes); unclassified cells, 7%. *Interpretation*: "destructive" process of bone marrow, possibly aleukemic reticulosis (13% histiocytes). *Bone marrow biopsy*: *Smears*: ratio of R.B.C. to W.B.C., 0.2 to 1. Differential count of the W.B.C.: mature N., 3.3%; metamyelocytes, 41.1%; myelocytes, 32.1%; myeloblasts, 20.1%; eosinophils, 1.8%; histiocytes, 1.5%. *Sections* showed marked cellular proliferation, predominating cell being the myeloblast. *Course*: Temperature came to normal a few days after admission. The patient was given a course of Roentgen ray therapy over the legs and scapulæ and there was improvement for about 2 months. He returned to the ward in relapse, again with fever. The liver and spleen were larger, the red blood cells and white blood cells lower. Shortly thereafter, he was admitted to another hospital, where again the diagnosis of myelogenous leukemia was made after bone-marrow biopsy. Postmortem study, however, showed generalized Hodgkin's disease (aleukemic reticulosis).

10. FLORENCE L.* Seen with Dr. E. T. Fisher, Hahnemann Hospital, Worcester, Mass. *Pre-biopsy diagnosis*: ? agranulocytosis; ? acute aleukemic myelogenous leukemia; ? lymphosarcoma of uterus with metastasis to bone marrow. *Biopsy diagnosis*: acute myelosis. *Final diagnosis*: myelosarcoma (chloroma); terminal aleukemic myelosis (Table 4).

11. GLADYS M. Seen with Dr. C. Lawson at Rhode Island Hospital, Providence. *Pre-biopsy diagnosis*: ? agranulocytosis; ? aleukemic leukemia. *Biopsy diagnosis*: acute aleukemic myelosis.

A single girl, aged 21, became exhausted in May, 1932, and increasingly weak during July and August, 1932. A tooth was extracted on August 5. The face became markedly swollen, and there was almost constant bleeding from the tooth socket for 3 days. Weakness and pallor became rapidly worse, and on August 12 the patient was admitted to the hospital. *Examination* disclosed extreme pallor which was of a sallow-yellow tint. Several petechial spots were present on the buccal mucous membranes and the hard palate. The spleen was felt 2 fingers' breadth below the left costal margin, although the liver was not enlarged. The *blood*: hemoglobin,

* This case will be more fully reported at a later date.

26 to 33%; R.B.C., 1,300,000 to 1,800,000; W.B.C., 3400 to 2800. Differential count: granulocytes, 73% (mature neutrophils, 2%; metamyelocytes, 5%; myelocytes, 2%; pre-myelocytes, 8%; myeloblasts, 57%); lymphocytes, 23%; monocytes, 2%; histiocytes, 2%. The red blood cells showed slight achromia and moderate change in size and shape. The blood platelets were very much diminished, with several bizarre forms. *Interpretation:* bone-marrow destruction, probably myeloblastic in origin. The *bone-marrow biopsy* (August 15, 1932) disclosed a ratio of W.B.C. to R.B.C. of 1 to 0.7. Differential count of the W.B.C.: mature neutrophils, 1%; metamyelocytes, 8.5%; myelocytes, 12%; myeloblasts and pre-myelocytes, 77%; histiocytes, 1.5%. Oxidase stain of the myeloblasts positive. *Diagnosis:* acute aleukemic myelosis. *Course:* The patient rapidly grew worse and died on August 24, 1932.

TABLE 4.—(CASE F. L.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<p><i>History:</i> female, aged 33. <i>Hysterectomy</i> (for menorrhagia), May 2, 1932. Large tumor adherent to uterus and left ovary, encroaching on left ureter. <i>Diagnosis:</i> ? sarcoma. July 15, 1932: "black and blue spots" of skin. August, 1932: bleeding from gums, pallor.</p> <p><i>Examination:</i> pallor. Gums swollen, spongy, bleeding. Few petechiae and ecchymoses.</p>	<p>May 1, 1932: Hemoglobin, 75%. R.B.C., 3.86. W.B.C., 8400. P., 70; L., 28; E., 2.</p> <p>August-September, 1932: Hemoglobin, 50%. R.B.C., 2.50. W.B.C., 6000 to 10,000. Platelets: rare.</p> <p>Red blood cells: achromia +; anisocytosis +; poikilocytosis +; polychromatophilia +.</p> <p>Differential count (author): mature N., 23%; metamyelocytes, 2%; myelocytes, 2%; myeloblasts, 48%; lymphocytes, 23%; monocytes, 2%.</p>

Clinical Diagnoses.

Original: ? Vincent's angina; ? purpura hemorrhagica; ? agranulocytosis.
Author's: aleukemic myelosis.

<i>Bone-marrow Biopsy.</i>	<i>Uterine Tumor.</i>
<p><i>Smear:</i> ratio of W.B.C. to nucleated R.B.C., 1 to 0.04.</p> <p>Differential count: mature N., 0; metamyelocytes, 3.7%; myelocytes, 0.3%; myeloblasts, 86%; histiocytes, 10%. Most of the myeloblasts were oxidase positive.</p> <p><i>Fig. 6.</i>—Photomicrograph of section of sternal bone marrow. (× 985.) Stuffing of marrow cavity with proliferating myeloblasts (<i>Myb</i>). Rare erythroblastic cell or megakaryocyte.</p> <p><i>Diagnosis:</i> acute myelosis.</p>	<p>Re-study showed growing invasive neoplasm of primitive cells with nucleoli and <i>oxidase</i> and <i>dopa</i> positive.</p> <p><i>Fig. 7.</i>—Photomicrograph of section of tumor of uterus removed at operation. (× 985.) <i>Dopa</i> stain. Note the neoplastic process composed of embryonic cells (myeloblasts), many of them showing a positive "dopa" reaction.</p> <p><i>Postmortem examination:</i> greenish tumors of gall bladder and about the left ureter; numerous enlarged lymph nodes; bone marrow involved throughout. Tumors, lymph nodes, bone marrow all stuffed with rapidly proliferating myeloblasts, almost all oxidase positive.</p>

Final Diagnosis.

Myclosarcoma (ehloroma); metastases (aleukemic myelosis).

12. SYLVIA W. B.I.H. 23483. *Pre-biopsy diagnosis*: ? Banti's disease; ? chronic myelosis. *Biopsy diagnosis*: ? myelosis. *Final diagnosis*: ? Banti's disease. A girl, aged 19, entered the hospital on March 17, 1932, complaining of easy bruising for several years, and of two severe hematemeses occurring in June, 1931, and January, 1932. *Examination* disclosed moderate pallor and a very large spleen extending upward to the axilla and downward to the pelvic brim. The *blood*: hemoglobin, 62%; R.B.C., 3,700,000; W.B.C., 2500; platelets, 170,000. Differential count: neutrophils, 79% (19% band forms); L., 15%; M., 6%. Quantitative bilirubin, 0.94 mg. per 100 cc. Roentgen rays of bones negative. B.M.R. normal. *Interpretation*: splenomegaly plus evidence of bone-marrow "destruction;" ? aleukemic myelosis; ? Hodgkin's disease; ? Banti's disease (hematemeses). *Bone-marrow biopsy*: hyperplastic marrow with abnormal islands of immature leukopoietic cells containing myeloblasts and histiocytes. Differential count of the W.B.C.: mature neutrophils, 3.3%; metamyelocytes, 34.3%; myelocytes, 18.7%; myeloblasts,

TABLE 5.—(CASE M. Z.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<i>History</i> : male, aged 2. Spontaneous ecchymoses 6 months. Increasing pallor 6 months. Swelling of gums 4 mos.	Hemoglobin, 56%. R.B.C., 3.07. W.B.C., 5300. Platelets, 24,000.
<i>Examination</i> : marked pallor. Ecchymotic spots. Generalized lymphadenopathy. Spleen palpable 2 fingers. Liver just palpable.	Bleeding time, 15 minutes. Reticulocytes, 7.4%. Red blood cells: achromia, 0; anisocytosis —; polychromatophilia —; average diameter, 6.95 micra. Differential count: N., 1%; L., 59%; M., 39%; B., 1% (2% ? lymphoblasts).

Clinical Diagnosis.

Obscure anemia.

<i>Bone-marrow Biopsy.</i>	<i>Further Findings.</i>
<i>Smears</i> : ratio of nucleated R.B.C. to W.B.C., 0.4 to 1. Granulocytic cells, 47.8%. Lymphoblasts, 43.2% (5 mitotic figures).	<i>Lymph-node biopsy</i> : proliferation of lymphoblasts destroying normal architecture of lymph node and invading the capsule.
<i>Sections</i> : infiltration of lymphoblasts and lymphocytes throughout marrow cavity.	<i>Postmortem</i> : generalized lymph-node enlargement. Most nodes showed "toxic" necrosis of germinal centers. One node showed stuffing with lymphoblasts.
<i>Fig. 8.</i> —Photomicrograph of section of bone marrow. (× 985.) Note the large number of lymphoblasts (<i>Lyb</i>) and lymphocytes (<i>Ly</i>) infiltrating the marrow tissue.	
<i>Diagnosis</i> : ? lymphatic leukemia; ? lymphosarcomatosis.	

Final Diagnosis.

Subacute aleukemic lymphadenosis.

17.5%; histiocytes, 12.3%. *Diagnosis*: ? aleukemic myelosis; ? Hodgkin's disease. *Course*: Marked regression in the size of the spleen occurred after 4 Roentgen ray treatments directed over that organ, the spleen at one time retreating under the left costal margin. The patient has since remained well, although she continues to present slight splenomegaly, slight anemia and leukopenia. The diagnosis still remains in doubt.

13. MORRIS Z. B.I.H. 8654 and 9446. *Pre-biopsy diagnosis*: obscure anemia; ? bone-marrow invasion. *Biopsy diagnosis*: lymphoid proliferation in bone marrow; ? lymphosarcoma; ? lymphatic leukemia. *Final diagnosis*: ? lymphosarcomatosis; ? lymphatic leukemia (Table 5).

14. ELLEN O'C. B.I.H. 22702. *Pre-biopsy diagnosis*: pernicious anemia; ? macrocytic anemia of other type. *Biopsy diagnosis*: hypoplasia of bone marrow, ? arteriosclerotic or senile. *Final diagnosis*: hypoplastic anemia, probably arteriosclerotic (Table 6).

TABLE 6.—(CASE ELLEN O'C.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<i>History</i> : female, aged 66. Weakness 1 year, increasing recently; loss of 10 pounds in weight; increasing pallor.	Hemoglobin, 68%. R.B.C., 2.78. W.B.C., 7800.
<i>Examination</i> : "pepper-and-salt" hair; tongue smooth at the edges; finger nails flattened. (No other positive findings.)	Platelets, 354,000. Mean corpuscular volume, 123.
<i>Gastric analysis</i> : no free hydrochloric acid after injection of histamin.	Red blood cells: no achromia, macrocytosis. Av. diameter, 7.9 micra.
<i>Icterus index</i> , 6. Bilirubin, 0.61 mg. per 100 cc.	Differential count: N., 26.5%; L., 62.5%; M., 2%; E., 8%; B., 1%.

Clinical Diagnosis.

Pernicious anemia.

<i>Bone-marrow Biopsy.</i>	<i>Course.</i>
<i>Sections</i> : generalized increase in fat cells; no megaloblasts seen; sclerosis of marrow vessels.	Large daily doses of parenteral liver extract without reticulocyte or red blood cell response. No response to large doses of iron. Patient has remained in about the same condition (8 months).
<i>Fig. 9.</i> —Photomicrograph of section of bone marrow. (X 870.) Note the marked increase in number of fat cells (sternal marrow). At the right is seen an arteriole, showing evidences of sclerosis.	

Diagnosis:

Hypoplasia of marrow, probably arteriosclerotic.

15. RUTH R. Seen with Drs. L. Blacklow and E. W. Small at Waltham Hospital. *Pre-biopsy diagnosis*: ? pernicious anemia; ? lymphosarcomatosis; ? aleukemic leukosis. *Biopsy diagnosis*: subacute (aleukemic) myelosis. *Final diagnosis*: subacute myelosis (Table 7).

16. EVA S. Seen with Dr. R. F. Bicknell at the Lynn Hospital. *Pre-biopsy diagnosis*: aplastic anemia. *Biopsy diagnosis*: lymphosarcoma invading bone marrow. *Final diagnosis*: lymphosarcoma with metastases causing "myelophthisic anemia" (Table 8).

TABLE 7.—(CASE R. R.)

<i>Clinical Findings.</i>	<i>Blood Findings.</i>
<p><i>History:</i> female, aged 40. Weakness 18 months, increasing. Sore tongue 6 weeks. Paresthesias 6 weeks. Loss of weight.</p> <p><i>Examination:</i> Extreme pallor. (Tongue normal; spleen not felt; lymph nodes not felt; vibratory sensation normal.)</p> <p><i>Gastric analysis:</i> no free hydrochloric acid (histamin not given).</p> <p><i>Icterus index,</i> 6.</p>	<p>Hemoglobin, 35 to 16%.</p> <p>R.B.C., 1.90 to 750,000.</p> <p>W.B.C., 4000 to 2200.</p> <p>Platelets, 150,000.</p> <p>Mean corpuscular volume, 115.</p> <p>Red blood cells: achromia absent; many macrocytes; average diameter, 7.88 micra.</p> <p>Differential count: N., 36.5%; L., 39%; M., 25%. (No abnormal white cells seen.)</p>

Clinical Diagnosis.

- ? Pernicious anemia.
- ? Lymphosarcoma with involvement of the bone marrow.
- ? Aleukemic leukosis.

<i>Bone-marrow Biopsy.</i>	<i>Postmortem Examination.</i>
<p><i>Smear:</i> ratio of W.B.C. to nucleated R.B.C., 1 to 0.1.</p> <p>Differential count: mature N., 0.4%; metamyelocytes, 1.2%; myelocytes, 3.2%; pre-myelocytes, 7.6%; myeloblasts, 69%; histiocytes, 17.6%; eosinophils, 1.6%.</p> <p><i>Section:</i> extremely cellular marrow, normal tissue replaced by proliferating leukopoietic cells, oxidase positive.</p> <p><i>Fig. 10.</i>—Photomicrograph of section of bone marrow. (× 985.) Note the crowding of the marrow with granulocytic cells, myeloblasts (<i>Mbl.</i>) and myelocytes (<i>Mye</i>), myelocytes predominating.</p> <p><i>Diagnosis:</i> subacute myelosis (aleukemic myelogenous leukemia).</p>	<p>Myeloblastic proliferation, patchy in type with overcrowding of normal marrow tissue.</p>

Final Diagnosis.

Subacute aleukemic myelosis.

17. NELLO L. Seen with Dr. Smith at the Quincy Municipal Hospital. *Pre-biopsy diagnosis:* ? aplastic anemia; ? lymphosarcomatosis; ? aleukemic leukosis. *Biopsy diagnosis:* aplastic anemia. *Final diagnosis:* aplastic anemia.

An unemployed boy, aged 17, was well until onset of severe epistaxes, beginning in January, 1934. He became progressively paler. At no time had he come in close contact with chemicals. *Examination* in March, 1934, showed, besides the pallor, a few ecchymotic spots on the legs and arms. There was no lymph-node or splenic enlargement and no icterus. *Blood studies:* hemoglobin, 35 to 25%; R.B.C., 1,190,000 to 1,060,000; W.B.C., 2000 to 1000; platelets, 100,000; reticulocytes, 1%; differential count of

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the white cells: N., 40%; L., 54%; M., 6%. He was transfused several times without relief. *Interpretation:* probably aplastic anemia—no etiologic agent discernible; ? lymphosarcoma invading the bone marrow; ? atypical aleukemic leukosis; ? osteosclerotic marrow. *Bone-marrow biopsy:* almost complete replacement of entire sternal bone marrow with fat cells. A few tiny islands of red cell and white cell growth present. *Diagnosis:* aplastic anemia. *Course:* Death after repeated transfusions.

TABLE 8.—(CASE E. S.)

Clinical Findings.	Blood Findings.
<i>History:</i> female, aged 51, housewife. Fatigue and weakness increasing during 2 years. Extreme weakness and pallor 3 months.	Hemoglobin, 22%. R.B.C., 1.00. W.B.C., 4500.
<i>Examination:</i> Extreme pallor. (Tongue normal, no icterus, no lymphadenopathy, no splenomegaly, no abdominal or other masses.) Several petechiæ of skin and mucous membranes.	Platelets, much diminished. Reticulocytes, 0.6%. Average R.B.C. diameter, 7.6 micra.
<i>Laboratory findings:</i> gastric analysis; no free HCl. Icterus index, 7. Stools, urine, etc., all negative.	Red blood cells: no achromia; anisocytosis +; poikilocytosis +; polychromatophilia 0. Differential count: N., 32%; L., 62%; M., 4%. (No abnormal or young cells.)

Aplastic anemia.

*Clinical Diagnosis.**Bone-marrow Biopsy.*

Smears showed few cells. *Sections:* hypoplastic marrow in most sections. One area of cellular hyperplasia consisting of uniform cells with many mitoses pushing aside and infiltrating normal marrow tissue. *Figs. 11 and 12.*—Low ($\times 300$) and high ($\times 1000$) power photomicrographs of section of bone marrow. Note the mass of proliferating cells infiltrating and invading the normal marrow tissue (NM). The proliferating cells are identified as lymphoblasts (LbL). A mitotic figure is seen (Mi).

Course.

No relief with large doses of iron, large amounts of liver extract parenterally, multiple transfusions.

Diagnosis: lymphosarcoma invading bone marrow, resulting in "myelophthisis" anemia.

18. RICHARD S. Boston Disp. 295953. *Pre-biopsy diagnoses:* splenomegaly? cause; ? thrombocytopenic purpura; ? Banti's disease; ? aleukemic myelosis. *Biopsy diagnosis:* chronic myelosis. A school boy, aged 14, had been troubled with black and blue spots since the age of 3 months and had had numerous examinations, always with negative results until July, 1934. At this time he complained of constant fatigue. *Examination* showed a large spleen extending to the umbilicus

and a few slightly enlarged lymph nodes. *Blood studies:* hemoglobin, 77%; R.B.C., 4,700,000; W.B.C., 3100; platelets, 175,000. Differential count: neutrophils, 50% ("band" forms, 6; myelocytes, 2); lymphocytes, 46%; monocytes, 2%; eosinophils, 2%; bleeding time, 3 minutes; clotting time, 5 minutes. All other clinical and laboratory examinations were negative. *Diagnosis:* splenomegaly? cause. History of ecchymoses and low platelet count suggestive of thrombocytopenic purpura. Spleen too large and white blood cell count too low for this condition. Banti's disease and aleukemic myelosis most likely. *Bone-marrow biopsy:* hyperplastic marrow with marked increase in activity of leukopoietic tissue; islands of myeloblasts. *Diagnosis:* chronic myelosis. The patient is being followed.

Discussion. 1. *The "Blood" Diseases in Reality Diseases of the Blood-forming Organs.* Until very recently, abnormalities in the red blood cells, white blood cells and blood platelets were uniformly spoken of as "diseases of the blood," "disorders of the blood," the "blood" diseases and the "blood dyscrasias." Emphasis was thus placed upon the changes which were found in the numerical and morphologic characteristics of the cells in the peripheral blood. Hematology was thus for many years a "peripheral" study, in which little note was taken of the fundamental changes in the various blood-forming organs.* Curiously enough, it was the study of the blood picture in various infectious diseases, chiefly by Arneith and Schilling, which brought home the fact to many that an increase in immature granulocytes ("shift to the left") was dependent upon "regenerative" activity of the bone marrow, with resultant changes in the peripheral blood. Study of the pathologic changes occurring in pernicious anemia had shown that the bone marrow was probably implicated.

It was furthermore becoming rapidly apparent that the blood picture might not be the final word in many diverse conditions, and that in certain instances it might even be misleading. The extremely variable blood picture in apparently identical cases of leukosis, the identical blood picture of many widely different disorders (hypoplastic anemia, pernicious anemia, certain cases of Hodgkin's disease, lymphosarcoma, etc.) served to bring this out forcibly. The "release" factor appeared to be as important in the production of the blood picture as did the actual formation and destruction of the blood cells, as could be seen from the study of the bone marrow in agranulocytosis, pernicious anemia and primary hypochromic anemia. The term "blood diseases" has thus gradually become modified to that of "diseases of the blood-forming organs." This should make profitable careful study of the various sites of blood formation in every instance in which the peripheral blood cells show marked disturbance either numerically or morphologically. In most instances, study of the marrow alone should provide the necessary information, although in certain cases biopsy

* It is related of Türk, a famous hematologist of 1880-1890, that when questioned concerning the pathology of a certain "blood" disease, he was offended, drew himself up, and said, "Sir, I am a peripheral hematologist."

of an accessible lymph node is even of greater importance. Correlation of the marrow picture with that of the peripheral blood should result in a better understanding of the physiologic pathology of the various hematologic disorders, so much so that after a certain number of these conditions have been studied, the blood picture alone will usually, by analogy, reveal the state of the marrow. With the gradual development of this fundamental knowledge, the science of hematology should certainly become more "central" than "peripheral" in nature.

2. *The Diagnostic Value of the Bone-marrow Biopsy.* The bone-marrow biopsy, in the above-reported series of cases, has proved of greatest value in the diagnosis of obscure cases of anemia. Many cases presenting anemia as an outstanding symptom fail to present sufficient findings either clinically or hematologically, to warrant an exact diagnosis. This is particularly true in the cases of leukemic leukosis, of which a number have been presented above. The majority of cases of "leukemia" (leukosis) have, in the author's experience, been associated with a normal or low white cell count, and not with a high white cell count, as is the ordinary teaching. Many of these cases have been misdiagnosed clinically and hematologically. Thus, if a large spleen is present, Banti's disease, or splenic anemia, is usually diagnosed; if the anemia is of the macrocytic type, pernicious anemia is the diagnosis; if petechiae and ecchymoses are present, purpura hemorrhagica is considered; and if there is a marked leukopenia with but few adult neutrophils, the diagnosis of agranulocytosis is almost always made.

It should be remembered that the leukotic process is composed of primitive, rapidly growing cells which tend to invade normal blood-forming tissue and thus prevent normal blood formation. In the bone marrow, this process (whether myeloid, lymphoid or monocytic) results in impaired formation of red cells, white cells and platelets. This results hematologically in anemia, leukopenia and thrombocytopenia. This triad should always, therefore, suggest bone-marrow "destruction." Usually due to a leukemic proliferation, it may be due to invasion by lymphosarcoma, myelosarcoma (chloroma) or other metastatic malignancy. Careful study of the peripheral blood will usually show, in the leukotic cases, either myeloblasts, lymphoblasts or histiocytes; certain cases, however, do not show these changes. In any event, it is in these obscure cases of anemia associated with leukopenia and thrombocytopenia that the bone-marrow biopsy has been most helpful in the formation of an exact diagnosis, and has demonstrated that even with an extremely cellular marrow, the peripheral blood itself may be almost devoid of cells. The definite diagnosis of leukosis (myelosis, lymphadenosis, reticulosis) has been of great value in ruling out Banti's disease, splenic anemia, pernicious anemia in certain instances, agranulocytosis, purpura hemorrhagica and aplastic anemia. It is

probable that many cases of "agranulocytosis" which have failed to benefit by therapy with nucleic acid derivatives are in reality instances of aleukemic leukosis. The same is probably true of certain cases called "purpura hæmorrhagica." Those cases of "pernicious anemia" which fail to respond to active therapy with the various potent extracts of liver usually turn out to be instances of leukosis. The diagnosis of "aplastic anemia" and "hypoplastic anemia" should for the same reason be suspected.

3. *Value of the Bone-marrow Biopsy in Further Studies.* As noted above, it is necessary to understand blood pictures from the standpoint of their fundamental physiologic background. The bone-marrow biopsy thus becomes a tool in the further study of cases of anemia. The use of the biopsy in the study of pernicious anemia, both before, during and after treatment, has been commented upon. It has been of help in understanding the mechanism of the action of liver extract, etc., upon the hyperplastic, megaloblastic marrow of the disease. With liver extract, there is gradual diminution in the apparently futile hyperplastic formation of embryonic cells and increase in the normal erythronormoblastic type of blood cell formation. The biopsy has already proved useful in the study of primary hypochromic anemia^{1,25} and of great interest in the study of Hodgkin's disease. Studies of the marrow in agranulocytosis have shown that in certain instances there is marked hypoplasia of myeloblastic tissue and that in other instances, the reverse is true. From these findings, Beck²⁷ has recently speculated that certain cases of agranulocytosis are dependent upon FitzHugh and Krumbhaar's²⁸ lack of a "maturation" factor and others upon the absence of a chemotactic factor. The chief value of the marrow biopsy must remain, however, in its capacity as an aid in the diagnosis of obscure hematologic conditions. It should be pointed out that it is of great advantage that the hematologist be, as far as possible, his own clinician, clinical pathologist and pathologist. In these studies, the author studied each case clinically, made the blood studies, performed the bone-marrow biopsy, and then studied the marrow smears and sections.

Summary. The blood picture is the end result of many complex factors which have to do with the growth, destruction and liberation of the blood cells from the various hematopoietic organs. Although the peripheral blood usually reflects more or less accurately the condition of the blood-forming organs, it is certain that greatly diverse blood pictures may be present in identical pathologic processes. Conversely, identical blood pictures may be associated with fundamentally different disorders. It becomes important, therefore, to study what is "behind" the blood picture, *i. e.*, in the hematopoietic organs. The bone marrow, as the chief blood-forming organ, must deserve greatest consideration, since most of

the so-called "blood diseases" either originate there or are associated with various abnormalities of growth within its confines.

Biopsy of the sternal bone marrow with a small trephine was performed in about 125 cases of diseases of the blood-forming organs. The criteria for cellular diagnosis, together with the findings in the miscellaneous group of diseases, are briefly discussed, and the diagnostic implications considered.

Many cases presenting obscure anemia are not susceptible of ready diagnosis, even after prolonged clinical and laboratory investigations have been made. The marrow biopsy has proved of greatest value in the diagnosis of these difficult cases. Particularly has it demonstrated that many cases of so-called Banti's disease, splenic anemia, agranulocytosis, aplastic anemia and pernicious anemia are in reality, instances of aleukemic leukosis. Anemia, leukopenia and thrombocytopenia are a triad of laboratory findings which point to a "destructive" ("myelophthisic") process in the marrow which is usually "leukemic" in type. Cases illustrating the diagnostic value of the bone-marrow biopsy are briefly described.

Although its chief function is diagnostic, the biopsy has proven of great value as well in appreciation of the "central" character of the blood picture. This has helped greatly in the understanding of the formation of blood pictures in various pathologic conditions.

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(Titles have been omitted for sake of brevity.)

SYSTEMATIC VARIATION IN THE HUMAN MENSTRUAL INTERVAL.*

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THE interval between the menstrual periods is not of constant length for many women and recent studies show that the 28-day lunar cycle type is found less frequently as more accurate information becomes available. Pratt *et al.* (1929) emphasize the variability of the menstrual interval and Geist (1930) and King (1926) show objectively the variation that may be found when an accurate record is kept of the periods of women who had previously reported themselves to be regular. Memory for time is poor and suitable data for statistical analysis require the making of a continuous written record. Any analysis of the data accumulated in most clinics would give inaccurate results for this reason. Papanicolaou (1933) has reviewed much of the literature in this field and the variability of menstruation as this function starts is shown by the study of Engle and Schelesnyak (1934).

The clinician and the endocrinologist may wish to know how much variation may be expected in the menstrual intervals of the individual as well as the variation between different women. The statistically inclined person will wish to know in addition how significant any variation found is, or, whether the variations found are those of chance fluctuation. Few of the published papers contain adequate data for the answer of these questions because the observations on different women are averaged together, or are too few to permit the computation of the extent of the variation.

An analysis of the variation in the menstrual interval must be made on a long record of the same individual. Two such records are available for a little more than 9 and 12 years respectively. One individual kept marked yearly calendars (I) and the other a fairly complete diary (IV). The records are nearly complete and believed to be accurate. In addition to these long records the length of the interval, its variation, the age of the subject and length of the record is given in Table 1 for 2 unreported subjects and for 9 of the subjects from King (1926).¹ Subject II is a secretary, III a graduate student and the activities of Subjects I and IV are given in Table 4.

The mean length of the interval is shown in Table 1 to vary

* Interval, as here used, is the number of days from the first day of one menstrual period to the first day of the next period.

¹ Part of the computations were made by Miss Francis Kuehler as a problem in the author's course on the Analysis of Biological Data.

from 24.8 to 34.3 days for these 13 women. The frequency of the intervals for the two longer records are given in Table 2. The variation of the periods for a given subject is measured by the standard deviation (σ) of the periods.¹ Table 1 shows this variation to vary from 1 to 4.8 days for these women. Another convenient index of the variation found in a single record is the coefficient of variation (*c.v.*) which expresses the standard deviation as a percentage of the mean. Subject J has the greatest variation of 14% and H the least variation of 4%. A variation from the mean time of 67% of the standard (0.67σ) would be expected in about one of every two periods, a variation from the mean equal to the number of days in the standard deviation would be expected to occur in about one of every three periods and a deviation from the mean of twice the number of days of the standard deviation would be expected only about 5 times in 100 periods. Such a variation of 2σ , or a greater variation, would usually be taken to show some disturbance beyond that usually occurring in the menstrual rhythm. For most of the persons reported in Table 1 a variation of 2 days would be expected about once in every 3 periods and would not be statistically unusual. However for Subjects II and J a variation of 5 days from the mean period would not be unusual and a deviation of 10 days would be the least that would be statistically significant. The former enjoys normal health and activity. Similar measurement from many different women would be necessary to establish norms for clinical use and these figures are given only to show the variation actually measured in 13 women living in average or superior economic status.

TABLE 1.—GENERAL INFORMATION, MEAN AND VARIATION OF MENSTRUAL INTERVALS.

Subject:	I.	II.	III.	IV.	A.	B.	C.	D.	E.	F.	G.	H.	J.
Age*	21	26	30	23	30	29	21	23	13.5	35	27	33	27
No. of years	12+	2-	3-	9+	9	7	8	5	5	3	7	3	4
No. of periods (N)	134	22	29	110	101	94	63	48	47	29	25	22	21
Mean in days	26.0	32.2	29.2	24.8	28.4	25.3	26.2	28.9	28.7	25.2	28.3	26.8	34.3
σ in days	2.3	4.8	2.5	1.7	2.2	1.8	1.7	1.7	1.7	1.5	2.4	1.0	4.8
c.v. %	9	11	9	7	8	7	6	6	6	6	8	4	14

The computations for subjects A to J based on data from King (1926).

* At the beginning of the record.

TABLE 2.—FREQUENCY OF MENSTRUAL INTERVALS FOR THE TWO LONGER RECORDS.

Days:	18.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.	31.	32.	33.	35.
Subject I	1	..	3	4	8	16	18	39	17	15	4	5	1	1	1	1
Subject IV	..	1	4	3	10	22	30	18	6	4	2

¹ When x is any one of N observations the mean, $M = \Sigma x/N$; the standard deviation, $\sigma = \sqrt{\frac{\Sigma(x - M)^2}{N}}$; and the coefficient of variation, *c.v.* = $100\sigma/M$.

The mean menstrual interval and its observed variation are slightly different for different women and we may next inquire whether these differences are statistically significant. The greatest difference of 9.5 days is found between the average intervals of Subjects IV and J. The significance of this variation must be evaluated in terms of the variation of both subjects and is obtained as the standard error of the difference,¹ which is 1.06 days. The ratio of the deviation to its standard error is 9.5/1.06 or about 9, and the normal probability table indicates that there is less than one chance in 10¹² of this difference being other than a statistically significant one. This is an extreme case of a difference obvious even without statistical treatment. A less extreme case would be the difference of 0.9 day between subjects B and C which is only 3 times the standard error of the difference and the probability table shows that this difference would be expected only once in about 370 cases. In general when the difference is twice the standard error of the difference, or greater, the difference is statistically significant and may be important in the clinic. When many periods are available the variation is more completely known and the standard errors are less. From the information in Table 1, a difference of a day or more between the mean menstrual interval of two women is to be regarded as statistically significant and in different women the humoral control or timing of the menstrual cycle is probably different to at least this extent.

The frequency of the menstrual intervals for Subjects I and IV is given in Table 2. The 18 and 33-day intervals of Subject I were caused by mumps and are not included in the following analysis. The 32 and 35-day intervals preceded pregnancy and support the suggestion of a missed period given by the Hotellings (1932). The 21-day cycle (Papanicolaou, 1933) hardly occurs in either record. The 20 and 27-day intervals in the 10th year of Subject IV were associated with a repair operation, the 22-day interval in the 6th year occurred while traveling and the 22 and 29-day intervals of the 2d year occurred during a rest period from excessive fatigue. The other large variations had no apparent explanation. The variation (σ) of Subjects II, III, G and J is greater than that of Subject I. The ultimate explanation of the nature and control of the menstrual cycle must account for variation of this magnitude. The knowledge of this variation, even from a few cases, may aid the clinician to discover the extent of the variation in other cases and to understand its origin.

¹ The standard error of the difference between two means = $\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$ where

σ_1 and σ_2 and N_1 and N_2 are the respective standard deviations and numbers of observations in the two sets of data. The probabilities obtained from the ratios are to be found in the several books or tables on statistical method.

The diary of Subject IV gives the hour of day of the onset of the menses in 9 cases, the average time of which is 9.53 A. M. If two occurrences late in the day are omitted the average is 7.56 A.M. If the observations of more diarists were available, it might be possible to make more precise statistical analyses.

Tinklepaugh¹ has suggested that the weekly rhythm of daily life may influence the monthly menstrual cycle and has supported his view with observations on change of daily weight and on the frequent occurrence of the onset of the menses with respect to the Sunday rest day of the week. Table 3, presenting the days of onset for Subjects I to IV, shows more occurrences near the week end.

TABLE 3.—THE FREQUENCY OF ONSET OF MENSES BY THE DAY OF THE WEEK.

Subject:	I.		II.		IIIA.		IIIB.		IV.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Sunday	20	15	5	23	4	20	6	21	16	15
Monday	15	11	6	27	0	0	2	7	12	11
Tuesday	26	20	5	23	0	0	1	3	22	20
Wednesday	18	13	1	4	0	0	2	7	9	8
Thursday	11	16	3	14	4	20	5	17	18	16
Friday	19	14	0	0	7	35	7	24	15	14
Saturday	14	11	2	9	5	25	6	21	18	16
χ^2	5.01		9.28		16.7		11.60		6.96	
P	0.54		0.17		0.01		0.08		0.33	

Except for slight difference in the length of leap years and from cycles that do not divide into 365 days evenly the proportion of onset days of the menses should be the same for each day of the week over a considerable period of time unless a systematic variation occurred. The Chi-square test² is appropriate to test whether the variation found from equal probability is greater than fortuitous variation and whether it supports the hypothesis of Tinklepaugh. From the computed value of Chi-square the probability (P) is obtained from the table of Fisher and when this probability is less than 0.05 the data would be considered to support the hypothesis tested. The values found are all greater than 0.05 and do not support the hypothesis except for IIIA in Table 3. Here the first report showed a very unequal distribution with respect to the day of the week. However, the second report added 9 more menstrual periods of the following year which filled in many of the vacancies of the table, thereby increasing the value of P to above the level of

¹ Based on a personal communication from Dr. O. L. Tinklepaugh of data to be published by him.

² When C is the observed frequency and E is the expected frequency
 $\chi^2 = \sum \left[\frac{(C - E)^2}{E} \right]$; the number of degrees of freedom, $n = N - 1$, and P is obtained from the table of χ^2 found in Fisher (1932), Chapter 10.

statistical significance. No change in the life of the subject took place to explain the difference in the 2 years and this indicates the necessity of having data over a considerable period of time in order to make meaningful comparisons. Further data will be necessary to adequately test the interesting suggestion of Tinklepaugh and data gathered on menstrual cycles should include the day of week of onset, or the calendar date, so that they may be examined from this viewpoint.

The year by year plot of the record of Subject I failed to show secular (long time trend) but did suggest a possible seasonal variation. To investigate this all of the data were plotted on a large scale graph so that the mean duration of the periods for each year was superimposed on the 26-day mean for all of the years. The individual deviations were then measured from this common reference value. A midvalue was found for the periods falling within each 10-day period of the year by adding algebraically all of the deviations within this 10-day period and then dividing the sum by the number. The averaging was repeated a second time with a 10-day interval beginning at the center of the previous 10-day intervals. The values obtained were plotted and gave a fairly smooth curve which was then smoothed and adjusted so that the standard deviations of each separate year from this line were least. This insured that the representative curve indicated the systematic variation during the entire record. This method of approximation was quicker and nearly as precise as the usual methods for the isolation of seasonal variation.¹ The final result was the smooth heavy line of Figures 1 and 2.

The menstrual intervals of Subjects I were more irregular during the first half of the year, tended to be longer by about 2 days during the summer months and were a little more than 2 days shorter than the average during the late fall of the year. As the seasonal curve is an average for all of the years it will not represent any one year exactly. Therefore, all of the variation is not to be explained in this manner as is illustrated for 8 years of the record in Figure 1. The years in which the data are incomplete or interrupted with pregnancies are omitted from the figure.

The variance (σ^2) was calculated for each year and the standard variation (σ'^2) for each year was computed in a similar manner, but measuring the deviations from the corresponding point of the curve of seasonal variation rather than from the mean. The ratio (μ) of these values (σ'^2/σ^2) for each year measures the agreement of the menstrual intervals for that year with the seasonal variation. The smaller this ratio the better is the agreement and with very good agreement the ratio would be nearly zero. The lack of complete agreement indicates the amount of variation due to other causes.

¹ For other methods see Rietz (1924) and Richards and Dawson (1927).

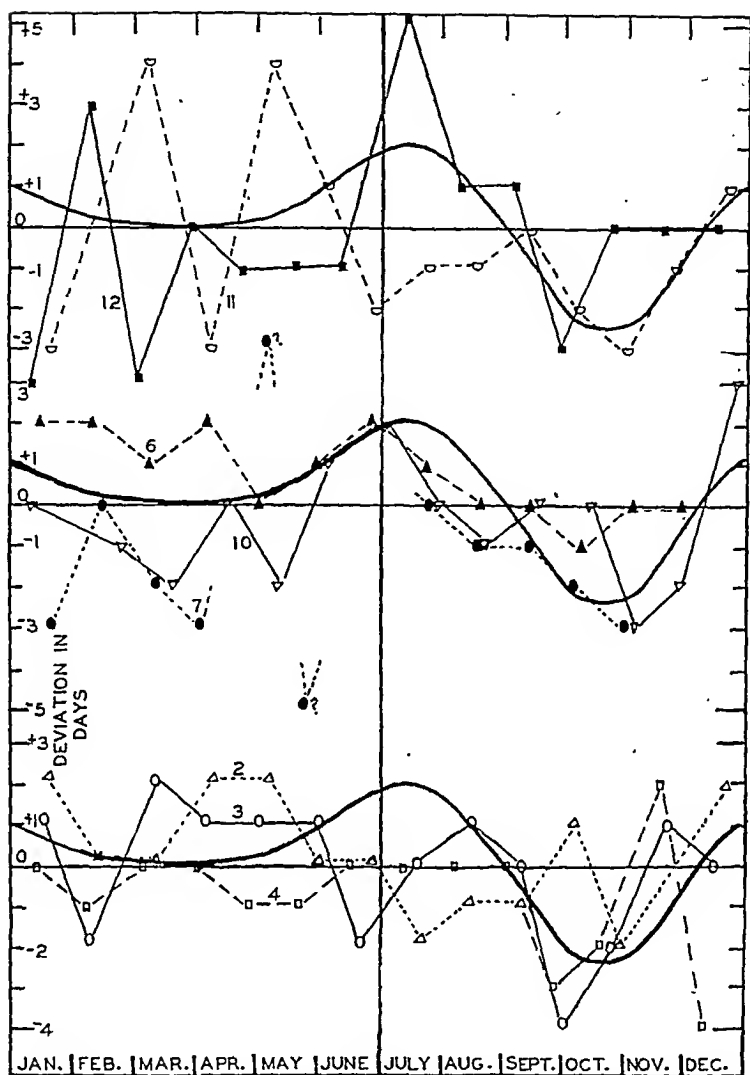


FIG. 1.—Systematic variations and observed variation of the menstrual rhythm of Subject I. The continuous heavy line (repeated in each graph) is the systematic variation and the observed variation is shown by the other lines numbered to correspond with the year in Table 4 (see text).

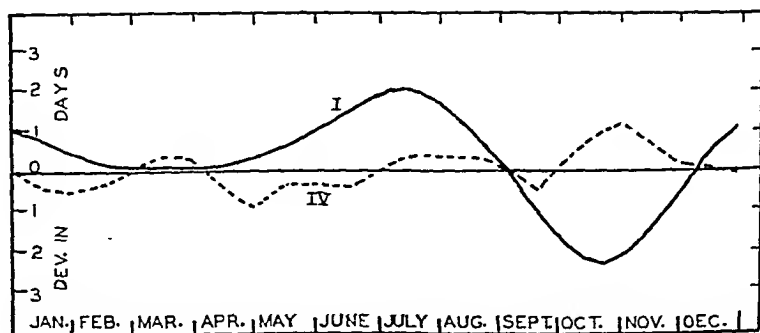


FIG. 2.—The comparison of the systematic variation of Subject I (continuous line) and that of Subject IV (broken line).

The ratios, Table 4, are less than unity for all of the years except the second, fourth and eleventh. The second year is out of phase with the seasonal trend. The seventh year shows good agreement except for the two marked fluctuations due to mumps marked by interrogation points on the graph (Fig. 1). The fourth year was the most uniform as half of the intervals were the same length as the mean and the twelfth year was the most variable especially during the summer months. The deviations of the seventh year may be due to traveling also those of the eleventh year. Except as marked in Table 4 or previously mentioned, the changes in the life of the subject do not throw any further light on the observed variation.

TABLE 4.—ANALYSIS OF THE DATA FOR SEPARATE YEARS.

A. SUBJECT I.

Year:*	S1.	S2.	M3.	H'4.	T6.	V7.	P8.	P9.	H10.	T11.	H12.	
Number	In 8	13	14	14	12	12	7	5	15	14	14	
Mean	24.6	26.1	24.6	28.1	29.5	25.0	27.2	26.5	26.1	25.6	25.7	
σ	...	1.71	1.69	1.61	1.43	3.45	2.77	1.85	1.66	1.97	2.39	
σ''	...	1.83	1.61	1.81	1.2	1.89	2.08	1.54	2.18	2.35	
Ratio μ	...	1.15	0.91	1.30	0.70	0.30	0.56	0.86	1.25	0.97	Av. 0.89

B. SUBJECT IV.

Year:*	S2.	S3.	S4.	TTc5.	TTc6.	Tc7.	MS.	HP9.	HP10.	
Number	10	11	11	In 7	15	15	15	7	6	
Mean	25.4	24.6	24.8	24.4	24.7	24.3	24.5	25.4	24.1	
σ	2.1	1.99	1.19	1.64	1.25	1.53	0.87	1.52	3.12	
σ''	1.87	1.73	1.04	1.61	1.23	1.39	0.89	1.27	2.07	
Ratio μ	0.35	0.76	0.77	0.97	0.97	0.83	1.02	0.67	0.45	Av. 0.77

$$\mu = \sigma'^2/\sigma^2 \text{ or } \sigma''^2/\sigma^2.$$

$\sigma'' = \sigma'$ less known deviations.

* Activities during the year are keyed as follows: In = incomplete, H = housewife, H' = housewife and also working in library, M = married, S = university student, T = traveling, Te = teaching, V = mumps, P = pregnant.

The general curve of variation is referred to as seasonal variation because that is a convenient descriptive term, but the variation may or may not be related to the seasons of the year. The shorter periods of the fall cannot be attributed solely to light as has been done with some of the lower animals (Wetham, 1933), because the return to average duration occurs when the days are shortest. The longer periods of the summer months may be a result of the higher temperature at that time. There was no change in the habits of the subject during the year that would explain this systematic variation of the menstrual periods.

The record of Subject IV shows no secular trend but does have a smaller cycle of seasonal variation which was isolated by the same method and is shown on Figure 2. Less variation is observed as would be expected since the standard deviation of Subject IV is less than that of Subject I. The curves are quite different with the longer intervals of Subject IV occurring in the late fall at the same time that they were shortest for Subject I. This difference suggests again that the systematic variations are individual differences and

not related to the season of the year. The year by year analysis of the record of Subject IV, Table 4, shows somewhat better agreement than that of Subject I.

Few records of sufficient length for analysis have been published or are available for comparison. There seems to be no such definite variation in the record of Subject A of King's (1926) paper. The number of observations in the other records are too few for detailed study. It will be interesting to know whether there is any evidence of systematic variation in the record of the special case covering 21 years of Papanicolaou (1933).

An adequate study of the variation of the menstrual interval will require accurate and consecutive records made over a considerable period of time for a number of normal women. The number of observations required will depend on the amount of the variation found. This variation must be stated in future published accounts as well as the length of the mean interval to permit close comparisons of the records of different subjects. When the data of many cases are combined from clinical records further analysis is impossible. The frequency of occurrence should be recorded for each day of the week and relevant data from the daily life of the subject should be added.

Summary. The mean length and variation of the menstrual interval is here given for 4 cases not previously published and for 9 cases from the literature. Some of the women showed a variation nearly 5 times greater than others within this small group. From the experience of this group of women a variation of 1 to 5 days may be expected and variations of from 2 to 10 days, depending on the variation of the individual case, indicate a definite departure from the normal variation. A variation of about 1 day in the mean intervals between 2 women is statistically significant and shows that there are marked individual differences in the menstrual rhythm. A systematic variation was found in the long records of two of the subjects. One menstruated less frequently in summer and more frequently in the late fall of the year. This systematic variation was followed more closely after interruption by pregnancy. The other subject menstruated more frequently in late spring and less frequently in late fall. The necessary formulæ of this kind of analysis are given. Further comparison of the results will have to await the publication of more data for analysis. It is believed that a knowledge of the individual variations in the menstrual rhythm will be of use to the clinician and will aid the study of the control of the female sexual cycle by the endocrine glands.

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THE DAILY REQUIREMENT IN HUMAN HYPOTHYROIDISM OF PURIFIED HUMAN THYROID HORMONE AT VARIOUS METABOLIC LEVELS.

A COMPARISON BETWEEN SPONTANEOUS MYXEDEMA AND CACHEXIA STRUMIPRIVA.

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INCREASED clinical interest in removal of the thyroid as a therapeutic measure in circulatory disturbances¹ has extended the necessity of using thyroid preparations for substitution therapy. In a previous communication² it was suggested that there existed appreciable differences between individuals with spontaneous and those with surgical hypothyroidism in their responsiveness to thyroid extract. Inasmuch as many such surgically treated patients are on the verge of cardiac decompensation, it is especially important to be able to judge with some accuracy the metabolic level which a given dose of thyroid will cause this type of patient to assume. Conversely, if it is desired to hold a patient at a certain substandard level of caloric turnover, it is necessary to know the daily requirement of thyroid hormone needed in such a case. Such knowledge offers an added safeguard to the sudden overburdening of cardiac reserve.

From the physiologic standpoint also, it is desirable to know how

far the spontaneous variety of myxedema resembles hypothyroidism produced by total thyroidectomy. It is the purpose of this paper to report studies of the daily requirement of thyroid hormone in cases of spontaneous and surgical myxedema, respectively, when adjusted to a steady state at various levels of metabolic equilibrium.

Plan of Study. The cases selected for observation were of two sorts. The first class consisted of 2 cases of spontaneous myxedema, one of whom had never been treated and the other of whom had relapsed after withdrawal of medication for 220 days. The second group consisted of 4 cases of typical myxedema following total ablation of the thyroid by Dr. E. C. Cutler.*

Following complete ablation of thyroid tissue the patients' basal metabolic rate was allowed to drop until the symptoms of myxedema became sufficiently severe to necessitate thyroid therapy. At this stage various patients had attained different levels of metabolism in accordance with the well known lack of correlation between basal metabolic rate and the clinical picture. The initial metabolism before treatment varied from -40% to -20% (Table 1). Inasmuch as this paper deals only with maintenance requirements at steady states of metabolism, it was not essential that the metabolic histories run parallel to each other. The presence of myxedema seemed absolutely certain in all these cases because of the invariable finding of clinical symptoms together with striking elevation of the blood cholesterol above the pre-operative level. The subsequent marked response to small amounts of thyroid hormone further validates the diagnosis of hypothyroidism.

TABLE 1.—DAILY CONSUMPTION OF HUMAN THYROID HORMONE AT VARIOUS METABOLIC LEVELS. (EXPRESSED IN MILLIGRAMS OF THYROGLOBULIN IODIN.)

Metabolic rate.	Spontaneous myxedema.				Surgical myxedema.				Spontaneous myxedema, Means and Lerman.‡
	Case 1.*		Case 6.†		Case 2.*	Case 3.*	Case 4.†	Case 5.†	
	Human.	Desiccated.‡	Human.	Desiccated.‡					
+10%	0.7	0.4	0.3	...	0.2	0.2	0.3	0.1	0.4
±0	0.6	0.2	0.2	...	0.1	0.15	0.3	...	0.1
-10	0.3	...	0.1	0.1	0.1	...	0.1	...	0.05
-20	0.3	...	0.1
-30	0.1	...	0.05
Av. initial B.M.R. before treatment .	-40%	...	-40%	...	-25%	-20%	-32%	-26%	...

* Treated with thyroglobulin from multiple colloid adenomatous goiter ("non-toxic").

† Treated with thyroglobulin from primary hyperplastic glands ("toxic").

‡ Calculated on the assumption that U.S.P. desiccated thyroid contains 0.2% thyroglobulin iodine.

In order to have a standard and fairly pure source of thyroid hormone, it was decided to use thyroglobulin extracted from human glands. These were obtained fresh after surgical removal and extracted with 0.02 normal sodium hydroxid. From this solution the thyroglobulin was repeatedly precipitated, redissolved and reprecipitated with dilute hydrochloric acid

* We owe to Drs. Cutler and S. A. Levine the opportunity of studying these cases after operation.

at the iso-electric point of the protein (about pH 5). The purity of such a product in terms of other protein has been tested by Dr. Saul Hertz,³ who found that it evoked antibodies to human thyroglobulin in rabbits, without producing antibodies to human serum albumin or globulin.

The source of the thyroglobulin used was of two sorts, namely primary hyperplastic glands ("toxic") and multiple colloid adenomatous glands ("non-toxic"). These two preparations of thyroglobulin will be referred to in this report as "toxic" thyroglobulin and "non-toxic" thyroglobulin, respectively.

The strength of the medication was gauged quantitatively in terms of total iodine. The experimental justification for total iodine as a measure of thyroid activity has been discussed by Lerman and Salter.⁴ These authors have also pointed out the variation in activity of various preparations of desiccated thyroid now on the market, which makes accurate estimation of thyroglobulin iodine desirable in quantitative clinical studies.

It is of interest that, when assayed by the method of Harington and Randall,⁵ the moiety of iodine apparently present as thyroxine was in the case of the "non-toxic" preparation 30% of the total iodine and in the "toxic" preparation 25% of the total. The use of these two types of human thyroglobulin must be borne in mind in judging the effects to be described.

Clinical Procedure. Determinations of the basal metabolic rate were made daily except Sundays (Benedict-Roth apparatus). In all cases the patients were hospitalized and remained in bed, except for toilet privileges. A preliminary series of determinations was made until a stable metabolic level had been attained. Thereupon, the administration of thyroglobulin was begun in a small daily dose which was continued until metabolic equilibrium had been established at a higher level. The daily dose was then increased and continued until a second plateau had been attained. In this way it was possible to correlate various levels of caloric turnover with the corresponding daily administration of thyroid hormone.

In order to insure ready assimilation of the medication, the iso-electric suspension of undenatured thyroglobulin was each day dissolved with a few drops of dilute aqueous sodium hydroxide and added to 60 cc. of orange juice. This procedure was carried out in all cases except Case 1 (spontaneous myxedema), in which instance the thyroglobulin was not alkalinized. Thompson⁷ pointed out that alkalinization of a peptide of thyroxine insures maximal absorption of the drug. This is in all probability due to a simple solubility effect (Lerman and Salter⁸). Inasmuch as Barnes and Bueno⁶ have shown that soluble thyroglobulin is rapidly absorbed from the intestine, the lack of alkalinization in the first case probably had no significant influence on the results obtained. The result of better assimilation, in any event, would merely tend to make the response obtained in Case 1 more closely approximate the responses obtained with the other patients.

Metabolic Data. The results of the determinations of metabolic response are presented in Table 1. Only the value attained at each equilibrium level is given, in association with the daily dose of thyroglobulin iodine required to maintain it. As was to be expected,

relatively more thyroid substance was needed to maintain metabolism at higher than at lower levels. By comparing these levels it is possible to calculate the rise in metabolic rate produced by each additional 0.1 mgm. of thyroid iodine given. These values are presented in Table 2, for two ranges of initial metabolic rate (as measured before treatment). For comparison, there are included in certain instances in these tables the metabolic effects attained with Armour's desiccated thyroid extract. Table 1 also gives data recalculated from values for desiccated thyroid given by Means and Lerman⁹ in spontaneous myxedema.

TABLE 2.—EFFECTIVENESS OF THYROGLOBULIN IODINE IN ELEVATING BASAL METABOLIC RATE. (THE INDEX SHOWS THE RISE IN METABOLIC LEVEL TO BE EXPECTED PER 0.1 MG. OF IODINE ADMINISTERED DAILY.)

	Range of initial metabolic rate before treatment.	
	Severe myxedema, -40 to -20.	Mild myxedema, -20 to ±0.
Increase in B.M.R. from previous level:		
Spontaneous myxedema:		
Case 1*	6.7	5.6
Case 6† (human thyroglobulin)	19.2	10.0
(desiccated)‡	20.0	
Surgical myxedema:		
Case 2*	10.0
Case 3*	10.0
Case 4†	5.3	
Case 5†	10.0

* Treated with thyroglobulin from multiple colloid adenomatous goiter ("non-toxic").

† Treated with thyroglobulin from primary hyperplastic glands ("toxic").

‡ Calculated on the assumption that U.S.P. desiccated thyroid contains 0.2% thyroglobulin iodine.

It will be noted that the data vary over 50% from the mean, although there are too few values to warrant serious statistical treatment. This variation, we feel, is not due to technical errors but represents rather the random variation to be expected in a series of biologic measurements of this sort. Fortunately, the values for surgical myxedema are in general intermediate between those for our two spontaneous cases. Although more observations are desirable for greater accuracy, the expense of prolonged hospitalization has necessarily limited opportunity for greater exactness.

Discussion. Of special interest is the relative effectiveness of thyroglobulin iodine at different levels of metabolism in the mild and severe stages of spontaneous myxedema. In both of the cases here studied, the response was more marked at lower metabolic levels, in accord with long-established clinical experience. Table 2 offers quantitative evidence of this qualitative observation. It will be observed from Table 2 that the permanent elevation of metabolic rate produced by a daily dose of a 0.1 mgm. of thyroglobulin iodine varied from 19.2 points to 5.6 points above the pre-

eeding stationary level. More specifically, the data may be grouped into (a) the mild and (b) the severely myxedematous cases.

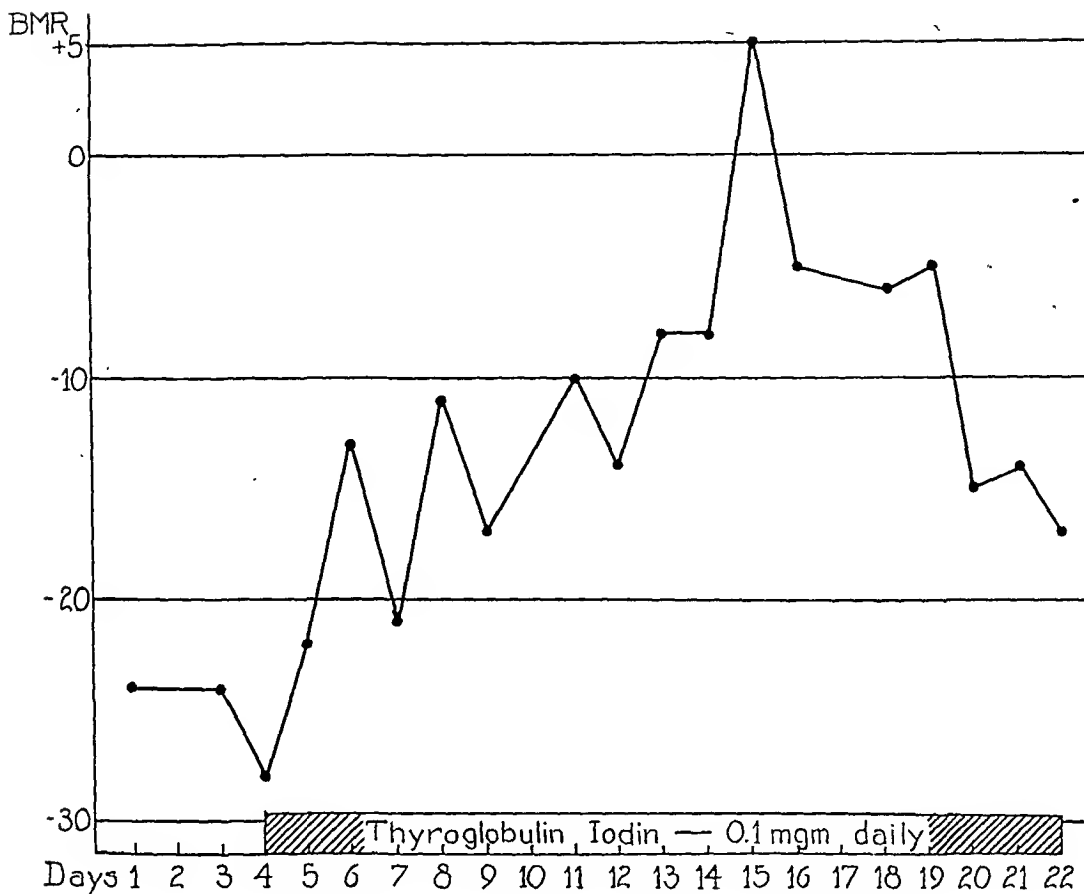


CHART I.—Response of human myxedema (surgical) to human thyroglobulin.

Thus, in the first case treated with “non-toxic” hormone the index for severe stage was 6.7 points per 0.1 mgm. of iodine as against 5.6 points per 0.1 mgm. of iodine in the mild stage. In the second case, treated with “toxic” hormone, the corresponding indices were 19.2 points per 0.1 mgm. of iodine during severe symptoms, as against 10 points when recovery was nearly complete. Whether the discrepancy between the effects of “toxic” and “non-toxic” preparations is due to chance variation or to actual difference in potency cannot be determined from the few cases reported here. Lerman and Salter⁸ have presented evidence which indicated no significant difference in the potency of these two preparations of thyroid hormone.

It is of interest that these extremes were found in the cases of spontaneous myxedema. In between these extremes are found the indices determined for the artificial surgical hypothyroidism, which ranged from 10 to 5.3 points per 0.1 mgm. of iodine. There is no

evidence from these figures to indicate that the response of artificial hypothyroidism to purified thyroid hormone shows any significant difference from that of spontaneous myxedema.

Means and Lerman⁹ have given average values of thyroid consumption in myxedema at three metabolic levels. These are reproduced in terms of iodine in Table 1. Our values in the 4 cases of surgical myxedema are quite similar. One of our cases of spontaneous myxedema (Case 6) likewise checks closely. Our other spontaneous case (Case 1) however, required nearly twice as much thyroid iodine while myxedema was slowly being relieved for the first time. Subsequently during ambulatory treatment with Armour's extract values approaching the general average were obtained.

In following the metabolic response of these patients while on a constant dose of thyroid hormone, a confusing feature was the tendency to overshoot metabolic equilibrium before settling back to a constant basal metabolic rate. This phenomenon is illustrated for Case 5 by Figure 1. Presumably the explanation lies in general structural and physiologic changes undergone by the organism as it recovers from the myxedematous state. It is conceivable that after maintaining a given metabolic level for many days, the requirement of thyroid hormone at this level may change. There was some evidence to suggest this in Case 1, but rigorous hospital control of the patient over the course of many weeks after recovery was not feasible.

Summary and Conclusions.—The effects of purified human thyroglobulin were studied in 2 cases of spontaneous myxedema and in 4 cases of artificial hypothyroidism surgically produced. These studies compare the responsiveness of myxedematous patients at various metabolic levels to purified human thyroglobulin. The results indicate that there is a fairly characteristic daily requirement of thyroglobulin iodine at any given level of metabolism. No definite discrepancy could be discerned between spontaneous myxedema and hypothyroidism produced by complete ablation of the thyroid gland.

In general, an addition of 0.1 mgm. of thyroglobulin iodine to the daily dose of hormone elevated the basal metabolic rate 10 ± 5 points.

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STUDIES OF GALL-BLADDER FUNCTION.

XII. THE COMPOSITION OF "WHITE BILE."*

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In the course of our earlier investigations of gall-bladder function we found that when the bile-free gall bladder of the dog became damaged there occurred a retardation of the rate of water absorption until, finally, instead of fluid being absorbed, fluids poured into the gall-bladder lumen.⁵ The fluid which we recovered had all of the physical characteristics of "white bile," or hydrops fluid, and was, as Rous and McMaster⁶ have stated, the result of the activity of the mucosal cells lining the lumen of the extrahepatic biliary system. Chemical analysis of this fluid showed it to contain approximately 100 milliequivalents per liter of chlorid, 2.5 to 5 milliequivalents per liter of calcium, and 60 milliequivalents per liter of CO₂. No bile salt was found in these specimens and the amount of cholesterol present was insignificant.

When a damaged biliary system becomes obstructed either in the cystic or common duct, the pent-up bile in the obstructed portion of the biliary tract is gradually diluted by the secretion of the mucosal cells and finally it becomes colorless, the bile pigment being either absorbed or undergoing a change to a colorless type of pigment. Whether an active acute infection is a factor in this

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mechanism, as Aronsohn¹ believes, is as yet controversial. It is, however, important that the mucosal cells of the gall-bladder wall, or the common duct, or both, be damaged.

During our investigations of the gall bladder and liver bile of the human being we were fortunate in securing at operation 15 specimens of hydrops fluid. In every case the cystic duct was found at operation to be occluded so that hepatic bile could not enter the gall bladder. In 2 patients we were able to secure the secretion from the gall bladder over a period of several days subsequent to operation. The study of this material forms the basis of the following report.

There has been a paucity of data on hydrops fluid, or "white bile," in the literature. Winternitz,⁸ Elman and Taussig,³ Bernhard,² Aronsohn¹ and Fowweather and Collinson⁴ have published data on the chemistry of "white bile," but in each instance the data are limited to a single or, at most, a few observations. In a number of other instances chemical studies have been of a purely qualitative character. In others no chemical data are given. Frequently deductions and generalizations are drawn which are unwarranted from the data the author apparently has had at his disposal.

Results. The original specimens obtained from our patients must be divided into two groups. In the first group (Table 1, 10 specimens), the chlorid concentration varied from 83 to 135 milliequivalents per liter, while the calcium concentrations of this group varied from 3 to 7 milliequivalents per liter. Cholesterol was present in only very small amounts, the highest being 28 mg. per 100 cc. Analysis failed to show the presence of bile salt as determined by the Gregory-Pascoe method. No analyses were made for bile pigment, since the material was colorless.

TABLE 1.—THE COMPOSITION OF "WHITE GALL-BLADDER BILE." LOW-CALCIUM GROUP.

Patient.	Calcium, mEq./L.	Chlorid, mEq./L.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
La.	6	99	0	
Fi.	6	100	0	
McC.	3	83	0	
Ca.	5	93	0	0
Ha.	7	133	0	0
Go.	4	122	0	Less than 5
Ma.	5	119	0	8
Wi.	3	132	0	2-4
Wa.	6	135	0	28
Da.	4	114	0	

In the second group (Table 2, 5 specimens) the material obtained from the gall bladder was sometimes colorless, but other specimens were somewhat milky in appearance, although they were not of the "milch-calcium" type described by Volkmann.⁷ The chlorid concentrations in this group varied from 106 to 140. The calcium

concentrations were definitely higher than in Group 1, varying from 11 to 44 milliequivalents per liter, thus containing calcium in concentrations varying from 2 to 8 times the normal serum level. The cholesterol concentrations tended to be on the whole somewhat higher than those found in the first group. No bile salt was found in this group.

TABLE 2.—THE COMPOSITION OF "WHITE GALL-BLADDER BILE." HIGH-CALCIUM GROUP.

Patient.	Calcium, mEq./L.	Chlorid, mEq./L.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
Le.	16	134	Trace	27
Ch.	25	140	0	Fluid 26 Fl. and ppt. 143
Pe.	32	127	0	15
Kr.	44	106	0	
Sc.	11	112	...	52

In Tables 3 and 4 are given the data on 2 patients in whom the gall-bladder secretion free from bile was studied over a period of several days. The data are similar to those reported in Table 1 except that in 1 patient the cholesterol concentrations were, as a rule, higher than those reported in Table 1, and with a single exception higher than those found at any time in the second patient:

TABLE 3.—THE COMPOSITION OF FLUID DRAINED FROM GALL BLADDER DAILY. PATIENT 1.

Date, 1934.	Chlorid, mEq./L.	Calcium, mEq./L.	P total, mg./100 cc.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
May 31	103.9	7.3	3.8	0	
June 1	97.9	7.3	3.0	0	
2	107.0	7.5	2.6	0	12.4
3	102.2	7.4	3.6	0	
5	102.2	6.8	2.9	0	30.8
6	101.5	6.2	3.2	0	
7	111.8	6.3	3.0	0	
8	120.9	5.0	2.5	0	
9	111.6	4.5	4.0	0	20.0
10	116.4	4.5	2.3	0	36.5
11	112.8	4.3	2.6	0	13.2

TABLE 4.—THE COMPOSITION OF FLUID DRAINED FROM GALL-BLADDER DAILY. PATIENT 2.

Date 1934.	Chlorid, mEq./L.	Calcium, mEq./L.	P total, mg./100 cc.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
Sept. 21	119.0	4.4	1.20	0	5.8
22	110.6	4.0	0.85	0	8.3
23	99.3	3.6	1.25	0	6.6
24	107.0	3.8	12.0	0	4.2
25	108.7	3.7	0.70	0	3.4
26	108.1	3.5	0.90	0	8.2
27	102.2	4.5	0.94	0	5.1
30	103.0	4.3	0.93	0	4.9
Oct. 1	91.4	4.3	0.90	0	6.8
4	115.7	4.5	1.01	0	39.0
5	108.1	4.6	3.20	0	11.7

Discussion. In a single specimen Winternitz⁸ found the chlorid concentration of "white bile" to be 0.761 gm. sodium chlorid per 100 cc. (130 milliequivalents per liter). Elman and Taussig³ found in 2 specimens a cholesterol concentration of 19 and 45 mg. per 100 cc., respectively, and in 2 others "macroscopic crystals" of cholesterol.

Bernhard² and Aronsohn¹ reported that specimens of "white bile" in dog and man which they had examined contained no pigment, bile salt or cholesterol. Bernhard found such fluids to contain approximately 10 mg. per 100 cc. (5 milliequivalents per liter) of calcium. Fowweather and Collinson⁴ reported in 6 cases of "white bile" that the calcium concentrations varied from (individual analyses not given) a trace to 15 mg. per 100 cc. (up to 7.5 milliequivalents per liter), and cholesterol values, from a trace to 130 mg. per 100 cc. These data are in general agreement with the more extensive data on "white gall-bladder bile" here reported. The composition of the "white bile" obtained from the gall bladders of the 2 patients from whom it was possible to obtain this over a period of days shows that the single specimen which we obtained was the result of the activity of the mucosal cells lining the gall bladder.

The higher calcium concentrations found in a few of the "white bile" specimens are not so easily explained. Since the cystic duct was occluded, the calcium must have come into the gall bladder with the fluid pouring in from its mucosa. The concentration at which it enters the gall bladder in the usual specimens of "white bile" is approximately at the serum level. The high concentrations found in several of these specimens which were not at all milky suggests that the calcium was present as other than the carbonate salt. Whether under certain circumstances, especially in the presence of infection, it may be secreted in a greater concentration is as yet unknown.

Summary. The "white gall-bladder bile" of the human is similar in its composition to that of the dog. It contains chlorid and, as a rule, calcium at approximately the serum level, the calcium concentrations being slightly more variable than the chlorid variations. The cholesterol concentrations were extremely low, while bile salt was absent.

In one-third of the specimens of "white gall-bladder bile" which we studied the calcium concentrations are considerably above the serum level. The cause of this calcium retention is unknown.

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THE DISTRIBUTION AND PROGNOSIS OF PULMONARY LESIONS.*

ASSOCIATED TUBERCULOUS AND NON-TUBERCULOUS.

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In physical diagnosis it has long been recognized that signs in the upper half of the chest are referable to tuberculous lesions, those in the lower half to non-tuberculous.¹ This generalization is applicable, however, only to the adult and that not without exceptions. In early childhood, especially in infancy, it is almost useless, and in adult life chronic tuberculous basal lesions do occur, though rarely.

It is only in the Roentgen ray film, with its capacity for exact definition of anatomical invasion, that it is possible to distinguish in distribution between tuberculous lesions that have been verified by a positive sputum and, on the other hand, chronic non-tuberculous bronchopneumonia,² established as such by prolonged observation, showing constantly negative tuberculin reactions and sputum negative for tubercle bacilli. On the basis of these essential differentiating criteria it can be established that there are characteristic sites of origin and spread in the chest for chronic tuberculous and non-tuberculous lesions, from which they depart only in extremely rare instances. Only in the first 6 or 12 months of life do tuberculous lesions originate in, or have their maximum severity in the cardiophrenic angle, the typical site of chronic non-tuberculous bronchopneumonia at all ages. There are also differences in Roentgen ray appearances, especially in later life, even when tuberculous lesions descend into the base.^{2,3,4}

* Read before the Association of American Physicians, Atlantic City, May 7, 1935.

In order more briefly and exactly to describe and discuss characteristic differences in site of tuberculous and non-tuberculous lesions, I have divided the lung field into six regions (Plate II, Fig. 2), of which the first three refer to the typical sites of origin of adult-type lesions in the upper third of the lung. The fourth takes in the middle third of the pulmonary cone. It is bounded above by an almost horizontal line and dips in a salient to the diaphragm in the midthoracic line. Within this Area 4 originate the majority of lesions of the childhood type after infancy; of these, the severe consolidations and excavations usually occur in Area 4 mesial, that is, on the posterior chest wall at about the seventh to the ninth rib levels, and the more benign occur chiefly at the anterior second and third interspaces. The lower third of the pulmonary cone contains the last two areas of the lung field, 5 and 6. In this lower third, Area 5 is bound mesially by the heart and mediastinum, below by the mesial half of the diaphragmatic contour, and laterally by an oblique line running from above at the hilum at the posterior level of the eighth or ninth rib, depending on the shape of the chest, to the base of the lung on the diaphragm at the midthoracic line. Essentially this area demarcates the paracardiac border from the anterior to the posterior chest wall, including particularly the cardiophrenic angle. This is the area of acute and chronic non-tuberculous bronchopneumonia; Area 6 is the region into which far-advanced lesions, both tuberculous and non-tuberculous may spread. See Plate II, Fig. 2.

The differentiation of the two lesions has long been an object of investigation;^{2,3,4} more recently I have been interested in their relations as they occur in the same chest.^{5,6,7} A detailed study has been made and is being continued, based on Roentgen ray observations on clinic patients over some 12 years, with medical histories of the patients and their families.

It has been found that extensive lesions in Area 5, and more particularly severe exacerbations of these non-tuberculous bronchopneumonias, observed in closely spaced serial films, do not intensify tuberculous apical lesions in the same chest, but are, in fact, commonly seen with retrogression of tuberculous lesions. This appears conspicuously in cases that heal with little or no treatment.

A series has been analyzed of 51 cases (Table 1) of tuberculosis under clinic observation that are known to have been sputum-positive and have become sputum-negative without treatment, or with rest short in proportion to the intensity and extent of the disease. These patients were otherwise unselected; the range in age was approximately from 3 to 55 years, only 2 being under the age of puberty; some were negroes. In this, as in other groups, it has appeared that the prognosis for the tuberculous lesion has been more favorable when it has been associated with a relatively extensive Area 5 lesion. On the other hand, it has appeared that the younger the patient, the greater his danger if the associated lesion

in Area 5 tends to heal. Indeed, relapse of tuberculosis in many cases has followed the healing of a lesion in Area 5, during the acute stage of which the apical lesion had retrogressed. In those whose sputum had become negative, but whose tuberculous lesion still appeared unstable, only relatively small cardiophrenic lesions were seen. In those patients whose sputum, once positive, had been negative for many years when first seen, extensive or residual lesions were usually found in Area 5.

TABLE 1.—SUMMARY OF ALL CASES OF SPUTUM + TUBERCULOSIS BECOMING SPUTUM — WITHOUT THERAPEUTIC PNEUMOTHORAX AND WITH LITTLE OR NO OTHER TREATMENT: OBSERVATION 1923 TO 1935.

Total number of cases	51
Age at first sputum + examination:	
Under 10 years	2
10 to 45 years	40
Over 45 years	9
Average number of years sputum — since last sputum +	8
Tuberculous lesion:	
Minimal	13
Moderately advanced	24
Far advanced	14
Cardiophrenic lesion:	
Severe	31
Marked	15
Slight	3

Age. When the sputum was first positive 40 of the 51 cases were between the approximate age of puberty and 45 years; only 2 were under 10 years; 8 were between 45 and 55, and 1 was 78. Of the far advanced cases, 10 were under 30 years.

Negative Sputums. Only 2 cases were listed as sputum negative when less than 2 years had elapsed since the last positive sputum. One of these is illustrated in Fig. 2.

Classification of Lesions. Of the 13 minimal cases, all had become sputum negative before Roentgen ray examination was made. It is probable that the lesions had retrogressed materially by the time these cases came under observation; 12 lesions had the linear appearance of old scars.

Of the 24 moderately advanced cases, 7 would be transferred to the far advanced group if all of the pulmonary damage were considered tuberculous. In the table, only that part of the involved area that is regarded as clearly tuberculous (upper two-thirds) has been made the basis of the grouping. Several of the minimal cases would similarly fall under moderately advanced according to standard classification.

As with the minimal lesions, some of the moderately advanced group were observed after the sputum had become negative, and therefore presumably after their tuberculous lesions had retrogressed somewhat.

Deaths. Of the 51 cases 5 are dead, all of causes other than tuberculosis. One died, aged 39, of a pituitary tumor. His sputum was consistently negative in 21 examinations for 5 years before death. Roentgen ray examination 1 month before death showed slight apical scars and a moderate basal lesion. Autopsy showed a scarred and calcified tuberculous lesion and a residual chronic non-tuberculous bronchopneumonia, which had been subject to marked exacerbations during the 5 years preceding death. One child had extrapulmonary (bone) tuberculosis.

One died, aged 42, of a "heart attack" 14 years after his sputum had ceased to be positive. When last examined, 7 months before death, the tuberculous lesion was minimal, the basal lesion severe. The sputum was negative 37 times, including 2 animal inoculations, in the 4 years preceding death. One child has moderately advanced, and one far advanced tuberculosis.

One patient died, aged 62, of apoplexy. He had been well and was looking for work when the stroke occurred. Sputum was negative for 3 years and absent for 1 year before death. His wife and 2 children had died of tuberculosis.

One died in his 64th year, 16½ years after the sputum had last been positive. The apical lesion was minimal and scar-like 7 months before death, while the basal lesion was severe.

One patient died, aged 82, of perforated gastric ulcer, 4 years after the sputum had last been positive, as determined by smear and animal inoculation. Postmortem examination showed a densely scarred apex typical of old tuberculosis, and an extensive chronic non-tuberculous pneumonitis of the middle and lower lobes with secondary moderate bronchiectasis. At least 1 child died of tuberculosis.

Lesions may be found in Area 5 in association with progressive tuberculosis, but they have been slight in extent or fleeting, or they have appeared after the tuberculous lesion was far advanced and well entrenched.

In infancy a non-tuberculous lesion may have a remote adverse influence upon tuberculous infection, even in the absence of an extensive or definite tuberculous lesion in the lung parenchyma.^{5,6} The effect, however, is apparently a purely mechanical one, the increased lymph drainage flooding nodes that were demonstrably grossly enlarged and, therefore, presumably the site of many young tubercles.² This flooding is most common as a result of bronchopneumonia, whether associated with measles or not. Aside from these cases, the occurrence of a non-tuberculous bronchopneumonia is associated in very young children, just as in older patients, with retrogression of tuberculous pulmonary infiltration. No evidence has been found that a non-tuberculous bronchopneumonia (Area 5 lesion) has aggravated an associated tuberculous pulmonary lesion at any age, and in the spontaneous retrogression of tuberculosis, a non-tuberculous element has commonly been a part.

It is evident that the method of examination is of the first importance in the study of such an interrelationship, which can be observed only in suitable roentgenographic views of the living. In the present study stereoscopic films have been synchronized to minimize the effects of cardiovascular movement, the importance of which has been discussed elsewhere.⁸ In the base of the lung, particularly, slight infiltrations may be overlooked or shadows may be mistaken for lesions in the blurring of trunk markings and of the cardiac border.² Hardly less essential to exact demonstration of slight lesions among the complex shadows beside the heart on the right, and on the left behind the cardiac contour, are multangular views. The patient is rotated so that the incident beam of the

Roentgen ray forms an angle of 5, 10, 15, 20, 30, 45 or 60 degrees with the sagittal plane of the body, the degree of rotation depending on the area to be thrown clear of the cardiac silhouette. Only in this way can consolidations in this region be exactly defined. Due regard is had to adapting the quality of the film so that it best records the critical density of a small lesion against a varied background of heart and vessels. The high-speed Bucky diaphragm⁹ may be used for observations of particularly obscure areas.

Moreover films must be closely spaced to catch the opposed rhythm that has been repeatedly observed in these studies, of apical retrogression with or shortly after basal spread, and of apical spread following basal retrogression. The retrogression of the apical lesion may not become obvious until after the paracardiac lesion has reached its peak, which may be a matter of 4 to 8 weeks. In retrogressive tuberculosis the Area 5 lesion characteristically persists while the tuberculous is decreasing, as suitably spaced films will show. There is, however, in many typical cases with favorable outcome a stage at which the paracardiac has become much less conspicuous while the apical continues to show marked retrogression. Films taken according to the rise and fall of symptoms may be made when the paracardiac infiltration is reaching its peak and then not again until both the apical and the Area 5 lesions have retrogressed materially. Such views would show only a coincident increase and decrease of both, and by themselves entirely misplace the emphasis and misinterpret the interrelationship of the two lesions.

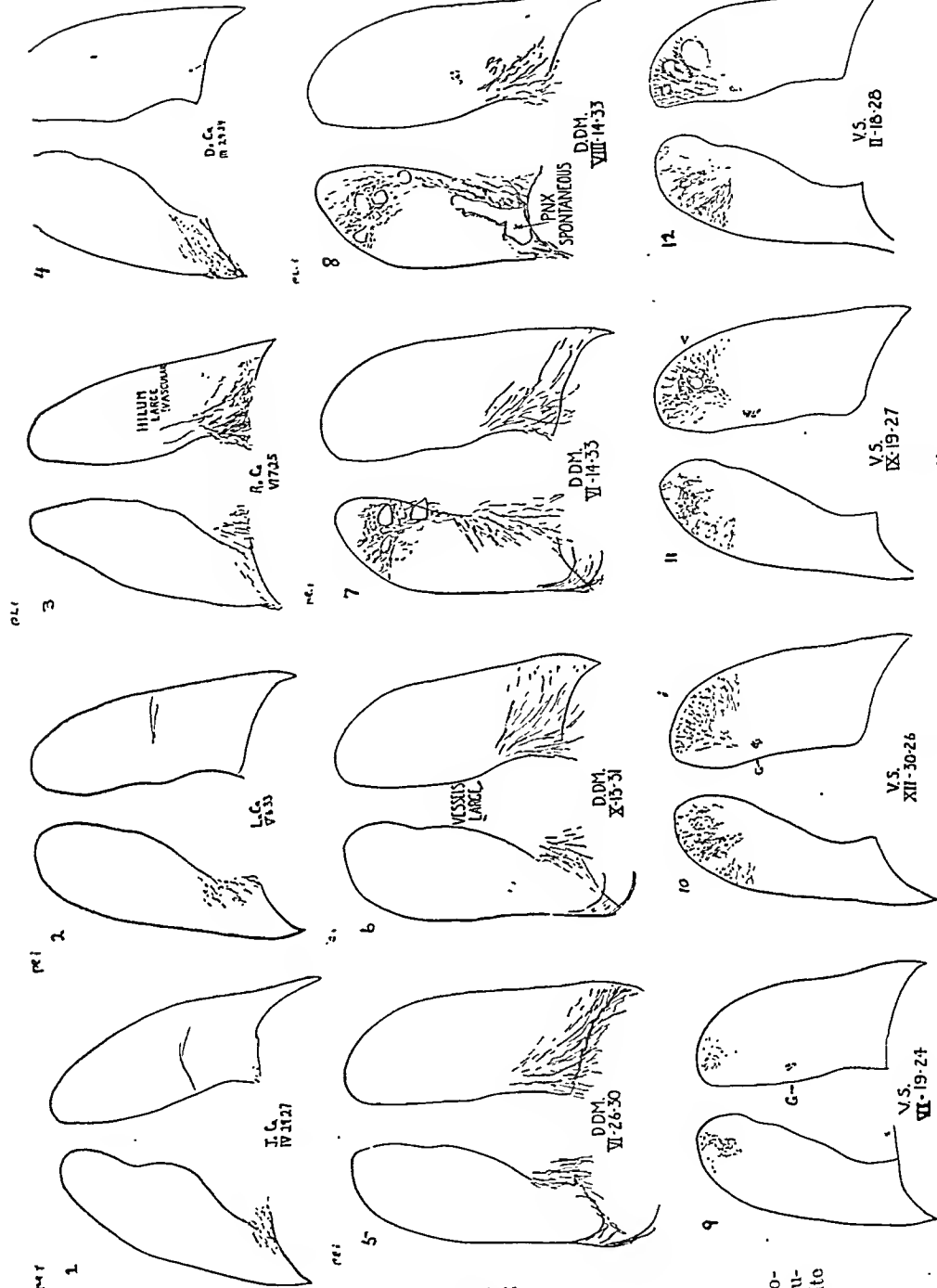
Of the cases that have been observed for years by this method, a large series has recently been reviewed and will be presented shortly.* A few typical cases are described here and are illustrated by diagrams traced from the films.

Cases of Uncomplicated Non-tuberculous Pulmonary Lesions. In Plate I, first row, are shown diagrammatically typical uncomplicated non-tuberculous lesions in 4 members of a white family with consistently negative sputums, a conspicuously high incidence of negative tuberculin reactions, and no known contact with tuberculosis. The father, aged 41 years and 2 months, on April 29, 1927 (Fig. 1), had occasional "colds," with some cough and expectoration. In March, 1929, he had a severe attack, with fever and weakness; the sputum, scanty, blood-streaked, was negative for tubercle bacilli. Sinusitis.

A daughter, aged 16 years and 2 months, on May 6, 1933 (Fig. 2), had for years suffered from attacks of cough. Sputum was negative on animal inoculation. Serial Roentgen ray examinations showed a fluctuating density obscuring the left cardiac border. Basal râles were heard in 1932 and 1933. With the exception of her parents, she was the only member of the family to have consistently positive tuberculin reactions from the time of her first examination, at the age of 8 years and 10 months.

In the third eldest child, a boy, aged 5 years and 1 month, on June 7, 1925 (Fig. 3), a non-tuberculous basal lesion was observed from 1925 through 1933; during this time his tuberculin reaction was consistently negative

* Exhibit, National Tuberculosis Association, June, 1935, and subsequent publication.



FIGS. 1, 2, 3, 4.—Non-tuberculous lesions in four members of a white family. See text.

FIGS. 5, 6, 7, 8.—Non-tuberculous basal lesions and lung abscess in young white adult. See text.

FIGS. 9, 10, 11, 12.—Progressive uncomplicated tuberculosis in young white adult. See text.

to 1 mg. O.T. until he was inoculated, in 1932, with killed tubercle bacilli, in a study carried on by a department of the Institute, when it became ++ to 1 mg. O.T. His sputum was negative for tubercle bacilli 8 times from 1926 to 1931 in smears and twice on animal inoculation. No spirochetes or molds. Gram-negative and Gram-positive diplococci and influenza bacilli reported on culture.

Clearing of infiltration was noted in films of February, 1927, as compared with those of 1925; subsequently wide fluctuations were seen in serial films. Many râles were heard in numerous examinations over the bases and sometimes throughout the lung. Cough was present with exacerbations from 1925, except for intervals of varying duration; expectoration was usually moderate, sometimes greenish. There was no history of other illness except pertussis in 1926.

The youngest child, aged 7 years and 7 months, on March 24, 1934 (Fig. 4), was first seen at 8 months. He has a history apparently dating from 1928 of acute attacks of coryza, cough, usually unproductive, sometimes with fever, sometimes with gastric symptoms; in good condition between attacks. Expectoration, greenish, was first reported in May, 1934. Roentgen ray, May 14, 1932, showed light spots at the base near the heart, right and left, which were interpreted as old bilateral basal lesions, probably non-tuberculous. The film illustrated in the diagram showed, on the right, prominent bronchi and a few strands in the lower third, and, on the left, a confluent patch, almost homogeneous, in the outer two-thirds of the area above the diaphragm (Area 6). Râles were heard in May, 1934, and again in May, 1935. The tuberculin reaction was negative to 1 mg. O.T. until it became ++ to 1 mg. O.T. in 1931 and again in 1932; it was negative to 0.005 mg. P.P.D. in 1934 (age, 8 years).

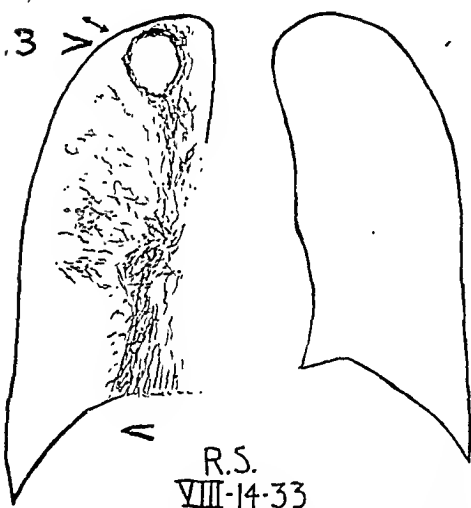
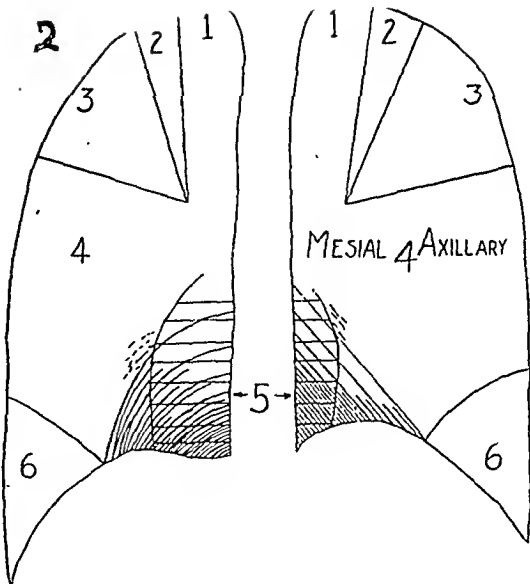
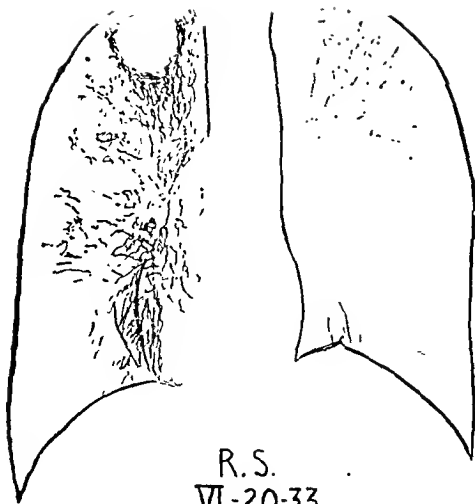
It is noteworthy that in this family of 6 children the tuberculin reactions were consistently negative for 37 person-years and fluctuated for 7 person-years. Positive sputum was never obtained from any member of the family. Elsewhere⁴ attention has been drawn to the family incidence of these lesions.

The second row of Plate I shows, in a white boy, aged 15 years and 8 months, on June 26, 1930 (Fig. 5), the development of an Area 5 lesion, with bronchiectasis, subsequent involvement of the upper two-thirds of the lung (pulmonary abscess) and death with brain abscess, November 4, 1933. Sputum was negative for tubercle bacilli 27 times from 1925 to 1933, as were also the bronchoscopic findings shortly before death. Tuberculin reaction positive to 1 mg. O.T., November 7, 1927; negative to 1 mg. O.T., January 23, 1929, August 1, 1930, and September 14, 1931.

History of pneumonia at 2½, 9 and 13 years. No known contact with tuberculosis. Hemoptysis, 1925; sputum occasionally blood-streaked. First seen in 1925 with occasional cough, expectoration and headaches. Cough, especially at night and mornings, from 1927, with "slight to moderate" greenish expectoration.

In June, 1930, the patient was 20 pounds underweight. In 1932, cough and expectoration were improved, with gains in weight, after treatment by postural drainage. A few râles were heard at the bases in two examinations, 1932 and 1933.

In June, 1933, after a long trip and exposure to rain, he had an acute illness, with high fever, pleurisy in left side, a loss of 15 pounds in 1 week, considerable cough and expectoration. Weakness and cough continued, with about 8 ounces of sputum daily. Roentgen ray showed consolidation in Area 5, right and left, and in addition, on the left, confluent spots in the middle third, and consolidation with excavation in the upper third. Two sputum examinations were negative. The patient was hospitalized, with a diagnosis of confluent bronchopneumonia, probable bronchiectasis and



> = DECREASE. < = INCREASE.

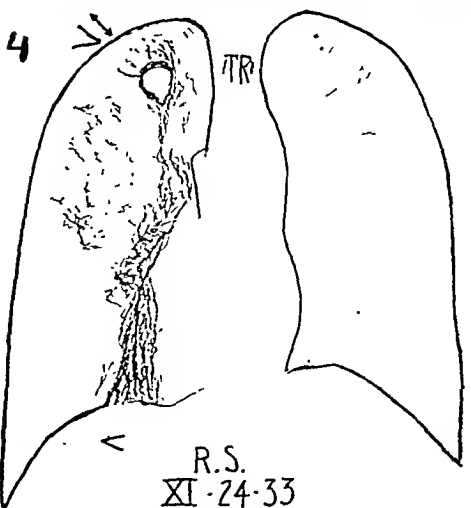


Diagram of 1 showing pathogenetic significance of several lung areas. Nos. 1, 2 and 3 are typical sites of adult tuberculosis. In No. 4 originate from the third to eleventh year characteristic tuberculous lesions, those postero-mesial often with cavity, those antero-axillary usually benign. No. 6 is an area of spread. No. 5 is the area of nontuberculous bronchopneumonia and of mixed tuberculous and nontuberculous lesions, both associated with apical healing. Intensity of shading corresponds to significance of distribution of persisting lesion.

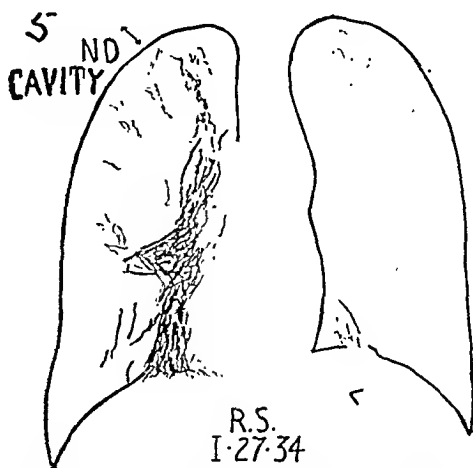


PLATE II.—Girl, white, aged 18 years and 5 months, June 20, 1933. Diagrams traced from films show retrogression of cavity and increase of Area 5 lesion in patient ambulant and later working. Sputum formerly positive became negative.

lung abscess. Bronchoscopy, July 3, 1933, by Dr. L. H. Clerf, found a large quantity of pus coming from the orifice of the left upper lobe bronchus, the mucosa of which was intensely inflamed. Culture of the pus showed chiefly *B. influenzae* and a few *Micrococci catarrhalis*; it was negative for acid-fast bacilli and spirochetes. Other sputum cultures (not bronchoscopic) showed *Strep. viridans*, *B. influenzae* and *M. catarrhalis* in three specimens; 7 sputum examinations were negative for acid-fast bacilli. There was no cardiac enlargement or displacement; no murmurs.

On November 1, 1933, the patient was again admitted to the hospital, unconscious, with a diagnosis of brain abscess or meningitis. He died, November 4, 1933. Postmortem examination showed partial healing of lung abscesses at apex of left lower lobe and dense fibrous scarring of both bases, with moderate cylindrical bronchiectasis traversing the scarred areas.

A Case of Progressive Uncomplicated Tuberculosis of Adult Type. In the last row of Plate I are shown diagrams from films of a boy, white, born March 27, 1912. These show uninterrupted progression of a tuberculous lesion with no lesion in Area 5 (see Figs. 30, 31 and 32 of Ref. 2). This boy's father died of pulmonary tuberculosis; his brother had a tracheo-bronchial calcification. Serial films showed that his lesions originated in and descended from the extreme apex. In June, 1924 (Plate I, Fig. 9), there was "soft" mottling down to the fourth posterior interspace, right and left, and a calcified hilum lymph node at the eighth rib, right. The tuberculin reaction was +++ to 0.01 mg. O.T. The weight was 106%. There were no symptoms and only transitory signs; a few râles were heard at one examination only.

The boy did not receive rest adequate to the increasing Roentgen ray density, probably because he looked very well, had good color and remained above normal weight, with steady growth and splendid physique. By March, 1928, sputum had become positive and the lesion far advanced, with consolidation and excavation. To continue with the serial review of the case:

On December 30, 1926 (Plate I, Fig. 10), the infiltration on the right above the clavicle was denser and there was a patch at the fifth rib at the axillary line posteriorly, and a calcified node at the seventh posterior rib and interspace. On the left there was moderately dense infiltration above the posterior fifth rib. Physical signs reported absent. The tuberculin reaction was ++ to 0.01 mg. O.T., the temperature normal and the weight 103%. Animal inoculations of throat swabs and feces were both negative. The general condition of the patient was apparently excellent, and the report of spread seen roentgenographically was not used to guide the treatment.

The patient was in a hospital, but ambulant, from August, 1926, to August, 1927. He was discharged as well enough for school, still having no symptoms and only trivial signs, but with Roentgen ray evidence of increased density in both apices with a small cavity on the right. Against our advice he went to school until February, 1928, when he came to the dispensary with slight cough of 2 weeks' duration. His sputum was positive. Impairment was heard over both apices, with a few fine râles over the right. He said he felt well; his weight was 101%.

In this case there is shown typical progression of an uncomplicated tuberculous infiltration to far-advanced extent. There was no infiltration in Area 5 until the tuberculous lesion was even farther entrenched than it appears in Fig. 12 (Plate I). In September, 1928, a small density occurred in the upper part of Area 5. It was trivial in relation to the extensive damage of both lungs, each of which showed sufficient tuberculous invasion to warrant a classification of far-advanced tuberculosis. The boy died, October 31, 1929.

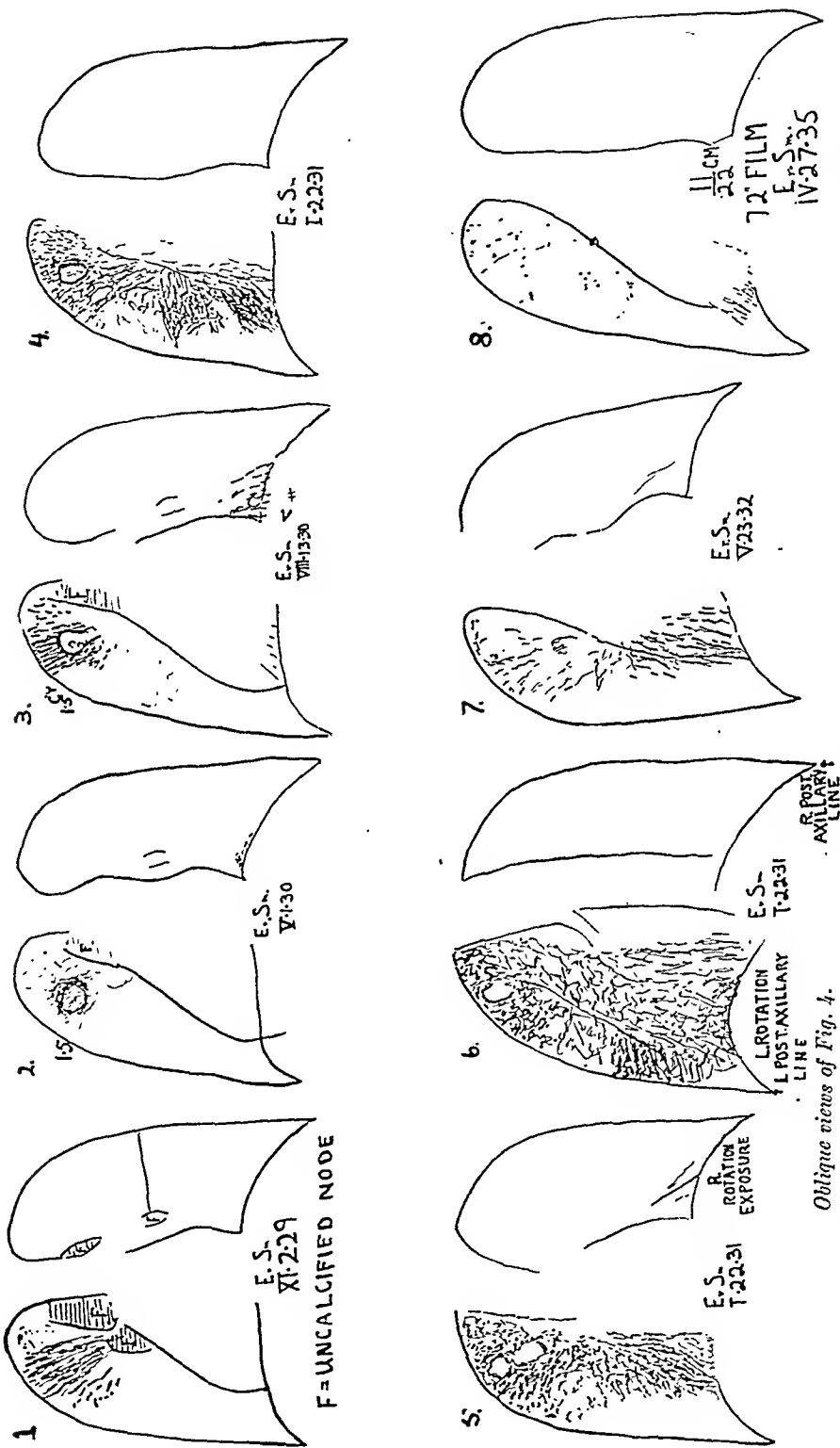


PLATE III.—Girl, colored, aged 10 years. Lesion in left apex fluctuating after appearance of small right paracardiac density (Figs. 1, 2, 3) and clearing after marked extension into Area 5 (Figs. 4, 5, 6). Fig. 7 shows marked retrogression of tuberculous lesion in left apex with persistence of "soft" basal density. Fig. 8 shows healed tuberculous lesion, persisting "soft" Area 5 lesion. Diagrams traced from films.

Two Cases of Associated Tuberculous and Non-tuberculous Pulmonary Lesions. Plate II illustrates diagrammatically these associated lesions in a girl, white, aged 18 years and 5 months, on June 20, 1933 (Fig. 1), when Roentgen ray examination showed, on the right, a few medium-sized ill-demarcated spots in the upper third, a few linear spots in the cardiophrenic angle (Area 5). On the left, at the posterior third and fourth interspaces there was a cavity, 3.5 cm. in size, surrounded by dense infiltration that descended as scattered and grouped large and medium-sized dense flocculent spots through the upper three-quarters of the lung field, chiefly mesial; in the lower quarter left there were linear spots upon the cardiac border. By August 14, 1933, after 6 weeks' hospitalization, the cavity had decreased in diameter, receding from the axilla mesially in a somewhat eccentric contraction, as is seen commonly with apical cavities associated with Area 5 infiltrations. The infiltration elsewhere in the upper three-quarters had decreased, that in the lower quarter had increased definitely, so that it now completely obscured the left cardiac border and spread out upon the diaphragm, causing a marked broadening in the apparent width of the heart shadow, especially where this passed over into the silhouette of the diaphragm. Instead of the acute cardiophrenic angle of June, there was a definitely obtuse angle, and the cardiac silhouette could be faintly perceived through the dense confluent linear spots that obscured the left border of the heart.

The patient continued ambulant and toward the end of the year began to work. The cavity had retrogressed further by November, continuing its eccentric contraction toward its mesial wall, and the infiltration elsewhere had likewise retrogressed, except that in Area 5 upon the cardiac silhouette and the adjacent diaphragm, which continued to increase slightly but definitely. This density upon the heart persisted into March, 1935, while the infiltration in the upper three-quarters continued to recede. In the last observation there were only a few dense spots in the upper three-quarters of the lung field. These were scattered except mesially, where they formed a light network.

Noteworthy in this case is the uninterrupted retrogression of the cavity after the patient got out of bed, at a rate not less while she was ambulant than when she was at rest. The only other consideration in the history is a tonsillectomy under local anesthesia in October, 1933. The films of June, August, November, 1933, and January, 1934, indicate that the operation had no relation to the rate of retrogression of the cavity and associated tuberculous infiltration.

Plate III shows diagrams of a girl, colored, aged 10 years, on November 2, 1929 (Fig. 1). At this time there was almost homogeneous infiltration in the left upper third and enlargement of associated nodes. In March, 1930, a small infiltration appeared on the right in Area 5. There was slight retrogression of the left upper third consolidation, but a cavity, 1.6 cm. in diameter, could now be perceived at the posterior fifth rib and interspace. The infiltration right and left fluctuated in extent until January, 1931, when there was a marked increase of infiltration throughout the left lung, extending to the diaphragm and wholly obscuring the left cardiac silhouette in the posteroanterior, and in both the right and left oblique views (Plate III, Figs. 4, 5 and 6). The patient had some rest at home and was hospitalized for 10 months, to January, 1932, with no additional rest. By March and May, 1932, reexamination showed a marked recession of the infiltration throughout. The apical tuberculous lesion was represented by a few scattered linear spots, but there were persisting grouped spots upon, behind and lateral to the cardiac silhouette, that is, in Area 5. The heart was now markedly enlarged. The electrocardiogram showed a left axis deviation, and there were physical signs of mitral insufficiency. By

April, 1935, the cardiac shadow had diminished slightly but was still definitely enlarged. In May, 1935, the patient returned with a recurrence of infiltration surrounding the cardiac apex (Area 5), a relapse of her non-tuberculous bronchopneumonia. The left apical tuberculous lesion was represented only by calcified spots and a few dense strands. It was apparently healed, in association with an unstable fluctuating or recurrent non-tuberculous bronchopneumonia.

Discussion. It is obvious that the conception of mutually opposed activity illustrated in the case histories shown in diagrams in Plates II and III, could not be based upon a few cases only, however striking they might be, but, as intimated above, has grown from detailed study for many years of a large series of cases. The 2 patients chosen for illustration are young women, one of them colored; age, race, sex, inadequacy of treatment were all unfavorable for the arrest of tuberculosis. Similar observations have been repeatedly made in patients of all ages, both sexes, white and negro, when serial films have been spaced closely enough to obtain exact information as to the distribution and intensity of lesions throughout the lung. These cases will be reported in detail as rapidly as possible.

A disadvantage of tuberculosis work, that it is not always possible to carry out adequate treatment, may be an advantage to the clinical investigator who takes the opportunity to follow the results of various treatments, and to observe the natural evolution of the disease. When there is a marked lesion in Area 5 it has been not uncommon to find patients suffering from malaise, cough, expectoration, in short the classical evidences of pulmonary tuberculosis, gradually show an improvement in strength and a decrease in symptoms while continuing ambulant and at work. The clinical improvement is accompanied by a retrogression of the apical density and a contraction of its cavities, while the basal density diminishes slightly, persists unchanged, or may even increase. Retrogression of the apical density may be extremely rapid, and uninterrupted or fluctuating concentric diminution of cavities may be seen in serial films occurring within a matter of weeks.* In brief, when there is a severe lesion in Area 5 an extensive and excavated apical lesion with positive sputum may retrogress to scarring and negative sputum in an ambulant patient in a manner excelling what would be expected with artificial pneumothorax or absolute rest in bed.

In closely spaced serial films made from many angles it has been frequently observed that increase of a basal lesion is shortly followed by diminution of the apical density with contraction of its cavities. In some cases of tuberculosis of short duration, a marked increase in an Area 5 lesion has been followed by complete scarring of an extensive, excavated tuberculous lesion. In cases of relapsing

* Healing in tuberculosis may occur uniformly throughout the lungs, and this appears to be the rule when there is a lesion in Area 5. In other cases that recover, healing is usually irregular, often with retrogression in one patch and simultaneous increase in another, perhaps closely adjacent area of the lung.

tuberculosis, on the other hand, retrogression of an associated Area 5 lesion has been observed until it is represented only by a few sharp strands, or fine unclouded diaphragmatic peaks. Following the basal retrogression the apical lesion increases. In the absence of adequate treatment, the future course of the lesion has appeared to have a relation to subsequent exacerbation of the lesion in Area 5, and to the extent, severity and permanence of this exacerbation. After the arrest of an apical lesion, cough and expectoration, consistently negative for tubercle bacilli, may persist for many years, and may cause disability as severe as the tuberculosis. As pointed out elsewhere, such cases are often mistakenly diagnosed "benign tuberculosis of middle age."^{7, 10, 11, 12}

Many factors play a part in the ebb and flow of the processes involved in tuberculosis. It is axiomatic, and a justification for research, that we have only an imperfect knowledge of the balance of factors that occurs when tuberculosis is arrested in the natural course of the disease or, indeed, when aided by rest. It is evident that the observations reported here could not be made by the methods of pathology, bacteriology, or other laboratory study, or by the usual clinical examination, but only by a method permitting exact exploration of the chests of the living. The criteria of roentgenographic examination, described fully elsewhere,² are based on earlier studies of excised lungs.^{8, 13} The writer's interpretation of the observations is that the lesions in the cardiophrenic angle are non-tuberculous, in whole or in part, that their exacerbations are characteristically accompanied or followed by retrogression of associated tuberculous lesions elsewhere in the lung field, and that in the series of cases studied this interrelationship has been a significant factor in "the natural tendency of the disease to retrogress." It is obviously impossible to measure or define exactly all the factors that may be concerned. It has long been well established that under experimental conditions a relative resistance against reinfection may be conferred by a previous infection with tubercle bacilli, but in general our conceptions of all that is implied in tuberculosis by the terms immunity, allergy, sensitization, are incomplete and confused, especially as applied to the complexity of natural conditions. The observations described above cannot be readily explained in the terms of immunology, but they appear to have a bearing on the wide problem of the resistance of the host to tuberculosis. It is hoped that other studies now in progress will throw further light on this phenomenon.

Summary. In serial Roentgen ray films it has been found that even in children, in whom tuberculous lesions characteristically do not originate in the upper third of the lung field, there is a sharp difference in distribution of the lesion between tuberculosis, on the one hand, and chronic non-tuberculous bronchopneumonia and bronchiectasis, on the other. Tuberculous lesions of childhood typically are situated in the middle third; those that are severe

and excavated are usually based on the posterior chest wall, the slighter ones on the anterior chest wall. Chronic non-tuberculous bronchopneumonia at all ages almost invariably originates and has its maximum severity in the cardiophrenic angle, whence during exacerbations it spreads along the diaphragmatic contour. Such lesions are associated with persistently negative sputum and, in children, with tuberculin reactions consistently negative for years.

In a comprehensive series of cases, sputum-positive lesions, of both childhood and adult types, that have become sputum-negative with little or no treatment have been observed in closely spaced multangular views. In such cases, tuberculous lesions in association with active and persistent cardiophrenic lesions have retrogressed rapidly, with contraction of cavities and disappearance of tubercle bacilli from the sputum. With complete arrest of the tuberculous lesion, the cardiophrenic lesion may fluctuate for years, with persistently negative sputum. On the other hand, in many clinic cases relapse of tuberculosis has followed healing of a lesion in the cardiophrenic angle, during the acute stage of which the apical or childhood type lesion had retrogressed. Lesions that according to the accepted classification are far advanced because the greater part of the lung is involved, including the cardiophrenic angle, have had a more favorable course than lesions of lesser extent and severity confined to the upper two-thirds of the lung fields, or invading the cardiophrenic angle only in terminal stages.

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ELECTROCARDIOGRAPHIC CHANGES DURING ENCEPHALOGRAPHY (20 CASES).

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CLINICALLY, pulse changes and other signs of vagus effects such as vomiting, pallor, sweating and variations in blood pressure have often been noted, during the injection of air in encephalography. In addition, there may be usually a slight rise in temperature, meningeal signs, headache and, during the passage of air upward, pain along the nerve roots.

The pulse changes have been described by various authors. In a typical description by Krause,¹ he points out that the pulse becomes slower, arrhythmic, small and weak and that pulse as well as accompanying respiratory changes for the most part soon disappear. Fay² states that the slowing of the pulse to 60 beats per minute is not uncommon. A number of observers have reported an initial acceleration of the pulse rate. Juzelevsky³ describes a case in which the patient's pulse could not be felt and the patient appeared to be on the verge of collapse. In almost every case of encephalography, however, there are minor signs of shock probably due to vagus stimulation.

Since we were unable to find in the literature any but clinical observations of the pulse changes, it seemed probable that simultaneous electrocardiography would yield further valuable information.

Technique. The patients were prepared by omitting lunch and giving a hypodermic injection of Magendie's Solution m. vii and Hyoscine gr. 1/150, from $\frac{1}{2}$ to $\frac{3}{4}$ hour before beginning the procedure. The patients were all in the sitting position in the encephalographic chair. Entry into the subarachnoid space was made *via* the lumbar route. At the same time the limbs were prepared for electrocardiography and a control electrocardiogram taken. In 3 cases, a record was taken every 10 minutes from the outset, at the first injection of air. In the remaining cases, tracings were obtained during the period when the pulse began to decrease in rate, and at intervals when the changes in pulse indicated that the more accurate record was necessary. The technical facilities at our disposal were such that continuous records were not feasible. Blood pressure was observed but not correlated with simultaneous electrocardiograms. Our readings, however, tended to confirm the already established facts, that the blood pressure rises during the injection of air and then gradually falls to normal within 8 to 36 hours.⁴ Pulse rates were noted in each case at 15-minute to 30-minute intervals for as long as the pulse remained below 60 after the injection of air was discontinued. This, of course, varied with the individual case.

Results. The results were compiled in the accompanying table.

TABLE 1.—ELECTROCARDIOGRAPHIC CHANGES DURING ENCEPHALOGRAPHY.

No.	Age.	Electrocardiographic changes.	Positive encephalographic findings.	Blood pressure.	Spinal fluid pressure (water).	Fluid/Air ratio.	Diagnosis.
1	19	Marked S. A. Occa. V. E. S. L. V. P. P2 and P3 inverted. Suggests interference with nervous mechanism	Cortical atrophy (left parietal).	100/90	110 mm.	125/95	Idiopathic or post-traumatic epilepsy.
2	12	S. A. In records Nos. 2 and 3 the Q-R-S waves are of lower voltage than in record No. 1 before encephalography	Normal	120/80	Low	102/82	Idiopathic epilepsy.
3	19	Migration of the pacemaker in Lead 3	Air in subtentorium. Cortical markings on both sides exaggerated	112/86	120	190/145	Idiopathic or post-traumatic epilepsy.
4	40	No appreciable change during injection of air. R ₁ low	Cortical atrophy (right parietes (?))	140/90	90	185/145	Idiopathic epilepsy.
5	20	Slight S. A. accentuated during encephalography with the production of bradycardia	Normal	115/70	70	145/110	Idiopathic epilepsy.
6	8	Considerable S. A.	Slight enlargement of 3d and 4th ventricles. Basal cistern dilated	110/80	Low	90/70	Idiopathic epilepsy.
7	13	First record: S. T. rate 105/min. The second record showed periods of phasic sinus slowing with an A-V nodal rhythm	No air in vent. system. Cortical markings good	100/80	60	120/115	Diffuse degen. Cerebral disease. (Congenital).
8	8	S. A.	Huacly dilated vent. system—symmetrical	124/80	150	Degenerative disease marked int. hydrocephalus.
9	41	Migration of cardiac pacemaker between the S-A and A-V nodes. Periods of S. A. with transitory nodal rhythm	Normal	110/80	100	Post-traumatic encephalopathy.
10	40	Rate 48/min. 2 hours after encephalography	Subarachnoid markings exaggerated and basal cistern enlarged	140/80	Low	200/165	Traumatic encephalopathy.
11	54	Sinus bradycardia, rate 38/min. R and T lower in second record than in first	Moderate dilatation of vent. Much air in subarachnoid space	150/90	Low	260/210	Traumatic encephalopathy. Lucas?
12	55	Low voltage in all leads. L. V. P.	Mod. dilatation of the vent. system. Much air in subarachnoid spaces.	140/80	Low	330/245	Alzheimer's disease.
13	31	Bradycardia of 50-60/min. Main deflection shows widening. Nothing in all leads. T ₁ inverted. R-T transition slightly abnormal in Leads 1 and 3	Slight asymmetry of lat. vent., left larger than right 3d vent. normal	112/76	100	150/125	Traumatic encephalopathy.
14	28	S. T. rate about 135/min. In Leads 2 and 3 rate slower with periods of sinus slowing, too far apart to be regarded as respiratory. Probably a form of sinus depression	Unusual collection of air in subtentorium bilaterally. Otherwise normal	160	145/115	Traumatic encephalopathy? Hysteria?
15	41	Marked bradycardia, 60/min. Shallow T in all leads	Slight depression of left lateral vent. Air over left cortex	138/133	230	98/83	Oxycephaly. Pituitary tumor
16	42	Left vent. preponderance	Vent. not outlined. Much air in subarachnoid space	120/90	110	Left frontotemporal. Neoplasm.
17	45	Sinus tachycardia, 100/min.	Intervent. septum displaced to right; left vent. displaced downward. Cortical markings absent on left. Much sub-tentorial air bilaterally	130/90	120	105/90	Left temporal neoplasm.
18	33	S. A.	Symmetrical and enormous dilatation of entire vent. system	60	250/220	Congenital communicating hydrocephalus.
19	56	No change	Symmetrical dilatation of the vent. system and much air in subarachnoid spaces	200/110	160	200/180	Cerebral arteriosclerosis.
20	35	A. F. and nodal rhythm	Slight dilatation of the vent. system. A little air in the subarachnoid spaces	100/70	220	125/115	Brain tumor? Pleuriglandular syndrome.

Key: S. A. = Sinus arrhythmia; V. E. S. = ventricular extrasystole; A. F. = Auricular fibrillation; L. V. P. = Left ventricular preponderance; S. T. = Sinus tachycardia.

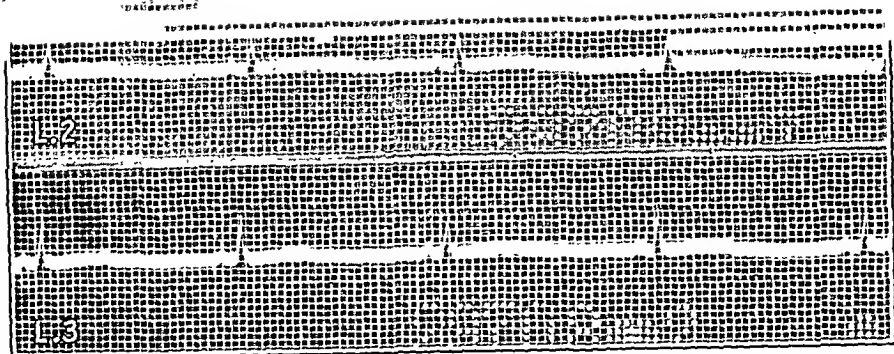


FIG. 1.—Case 2. Lead 2 shows low voltage and bradycardia, and Lead 3 a sinus arrhythmia in addition.
This and the following records were taken during encephalography.

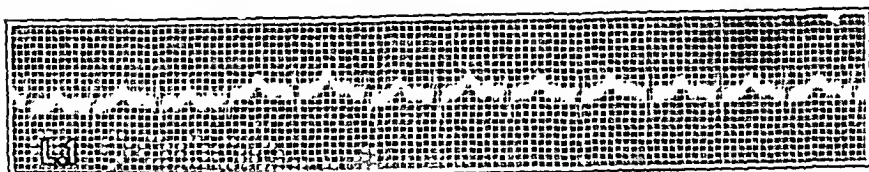


FIG. 2.—Case 7. Sinus tachycardia, 165 per minute.

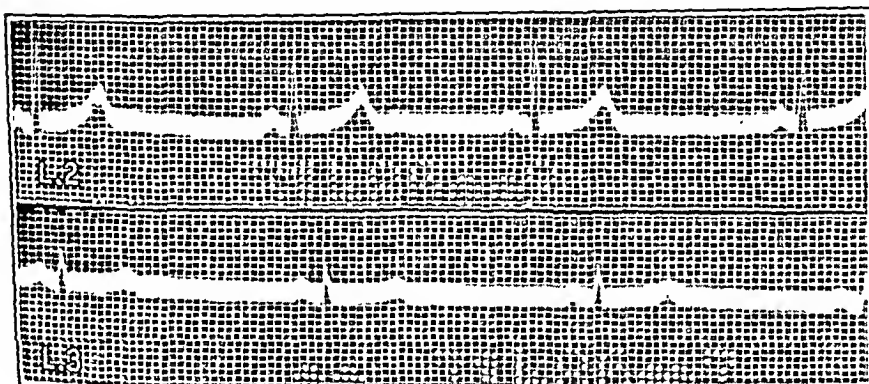


FIG. 3.—Case 11. Sinus bradycardia with R_3 and T_3 lower in Lead 3.

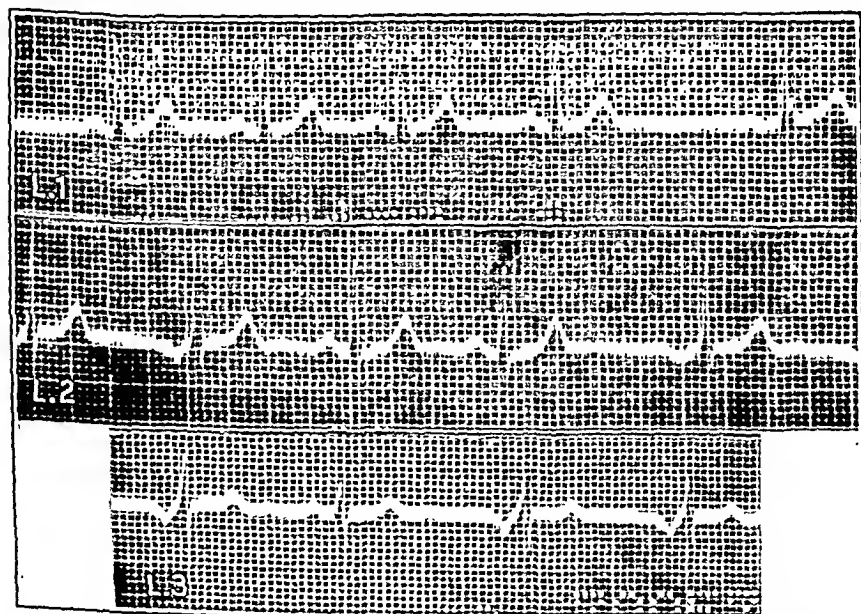


FIG. 4.—Case 9. Records show migration of pacemaker between $S-A$ and $A-V$ node.

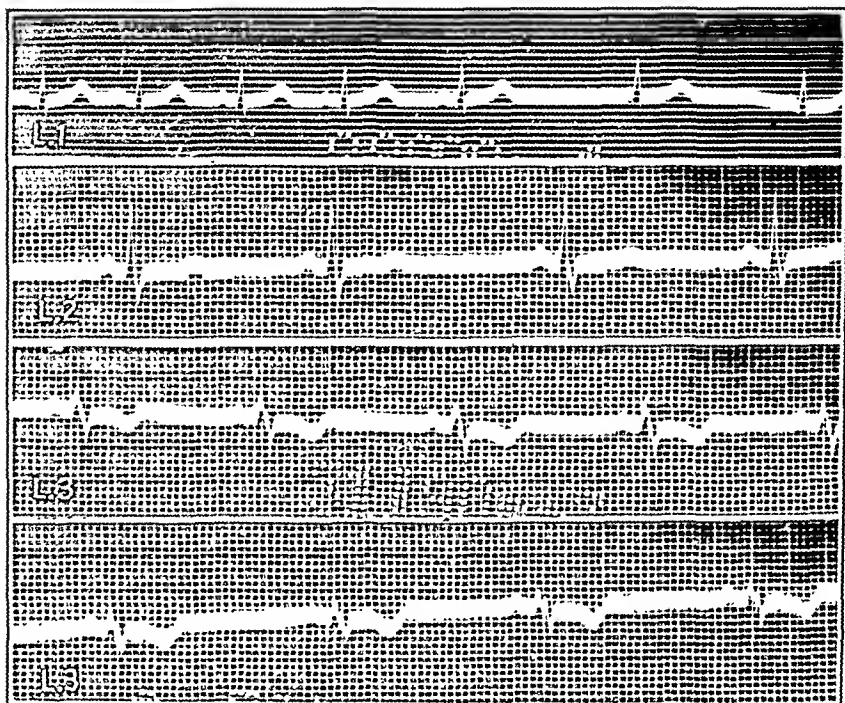


FIG. 5.—Case 13. Lead 1 shows sinus arrhythmia; Lead 2, bradycardia; and Lead 3, notching, T_3 inverted and notching with widening of $Q-R-S$ complex low voltage.

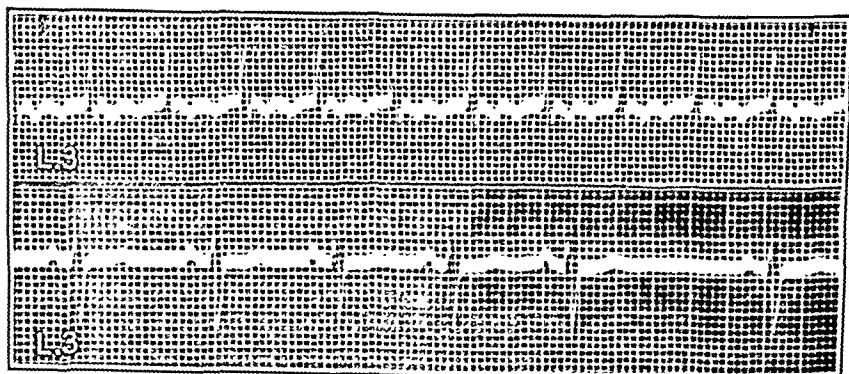


FIG. 6.—Case 14. A, Sinus tachycardia; B, phasic sinus depression.

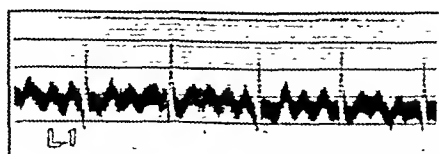


FIG. 7.—Case 20. Auricular fibrillation.

To summarize the results listed in the table it may be pointed out that the most frequent electrocardiographic change was that consequent-upon stimulation of the pacemaker, *i. e.*, in 13 cases. Of these, at one or another time during the procedure, 7 showed sinus arrhythmia, 5 showed sinus bradycardia, 2 phasic sinus slowing, 3 sinus tachycardia, and 2 showed a combination of these changes. The next most frequent variations was that consequent upon migration of the pacemaker. Of these, one showed auricular fibrillation (though impure flutter was seriously considered), two showed migration of the pacemaker between the *S-A* and *A-V* nodes. Next in frequency were changes indicative of dominance of the *A-V* node or lower ventricular foci. Of these, there were 3 cases of transitory nodal rhythm and 1 case of ventricular extrasystole. Five cases showed no appreciable change. In 6 cases the bradycardia lasted for 6 hours and then gradually returned to normal.

From these records, the conclusion may be drawn that the majority of the changes are to be attributed to excessive vagus stimulation. This is correlated with the other clinical manifestations of vagus origin. In the 1 case in which auricular fibrillation occurred, this change appeared immediately coincident with the first withdrawal of 15 cc. of spinal fluid, before any air had been injected. What the mechanism in this instance was, we are unable to say. It may have been due to a sudden change in intracranial pressure.

In view of these changes, it is interesting to consider whether or not, interference with the conduction mechanism of the heart might possibly be a factor in encephalography death, especially in those cases where the difference between the amount of fluid removed and air injected is very small and theoretically too little to accommodate air-expansion or air-irritation. The following case of encephalography death is of interest in this connection.

Case Abstract. A man, aged 55, was admitted to the Mount Sinai Hospital on September 29, 1928, with the complaint of weakness in the left upper and lower extremities of 6 months' duration, together with failing vision and personality changes.

Examination. Showed apathy, mental torpor, pyramidal tract signs and weakness on the left side, coarse tremor of fingers of the right hand, and bilateral papilledema and hemorrhages. The blood pressure was 140/85. Laboratory findings were negative. The clinical diagnosis was neoplasm of the right cerebral hemisphere, post-Rolandic in location. Cardiac rate and rhythm normal. Heart sound of poor quality.

Course. On October 5, 1928, at 3.00 P.M., encephalography was performed; 100 cc. of fluid was removed and 100 cc. of air was injected. The patient became ashen and cyanotic. At 6.10 P.M. the pulse was 40. Hands cold. At 11.00 P.M., the patient was in complete coma, breathing stertorously and moribund. The impression clinically at that time was questionably that of hemorrhage into a neoplasm. The next day at 8.20 A.M. the temperature mounted to 107 and the pulse was imperceptible. The patient died 15 minutes later, approximately 17½ hours after encephalography. The left cerebral ventricular system had been well visualized, was displaced to the left and was moderately dilated. The third ventricle was visualized and displaced a distance of ½ inch. No autopsy was obtained.

Inasmuch as anatomic verification of the brain's condition was not possible, it cannot be stated with certainty that there was not a hemorrhage into a neoplasm. However, the lapsing into coma 8 hours after encephalography together with the profound bradycardia and obvious cardiac death makes it necessary to consider the possibility of excessive vagus stimulation in a patient in the sixth decade of life and whose heart sounds were recorded as weak.

Summary. Twenty cases of simultaneous encephalography and electrocardiography are presented with a study of the changes in the cardiac conduction mechanism. The most common changes are those consequent upon stimulation of the pacemaker through the vagus: sinus arrhythmia, sinus bradycardia, phasic sinus slowing, sinus tachycardia, migration of the pacemaker between the *S-A* and *A-V* nodes, transitory nodal rhythm. In 1 case ventricular extrasystole was observed and in another auricular fibrillation. In 1 fatal case following encephalography the death was probably cardiac and followed the excessive injection of air with subsequent bradycardia and collapse at that period when most cases begin to show a return to normal rate. The findings are correlated with other clinical manifestations of vagus stimulation.

We wish to express our gratitude to Dr. I. Roth of the Mt. Sinai Hospital, and Dr. S. P. Schwartz of Montefiore Hospital for their generous coöperation in the reading of the records.

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FURTHER STUDIES IN CALCIUM AND PARATHYROID THERAPY IN CHRONIC ULCERATIVE COLITIS.

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IN 1931 we reported¹ the results of calcium and parathyroid therapy and certain observations regarding the diffusibility of serum calcium in a series of 13 patients with chronic ulcerative

colitis. The rationale of this form of therapy was believed to rest upon the beneficial effect of calcium on the following existing conditions: *a*, Nutritional change in the tissues, with or without a disturbance of calcium partition; *b*, spasticity of the colon; *c*, hemorrhage. Eleven of the 13 patients became clinically well in from 4 to 8 weeks and, at the time of the previous report, 10 of these had been observed over a period of from 1 to $2\frac{1}{2}$ years. The mucosa of the lower bowel had resumed a normal appearance in 8, and in 2 symptoms had returned for a short period of time.

In view of the chronic nature of this condition and its marked tendency toward spontaneous remission and relapse, the efficacy of any form of therapy can be properly evaluated only after a prolonged period of observation of individual cases. We have been able to study 8 of the original series of patients over a period of 4 to 6 years and have applied the same therapeutic procedure in 16 additional cases, observed over periods varying from 6 months to 4 years.

Method of Treatment. The plan of treatment is essentially the same as that described in the previous report and includes: (1) a cellulose-free, non-irritating diet; (2) such drugs as belladonna and kaolin; (3) calcium gluconate and parathyroid extract. As was previously emphasized, calcium is best absorbed when the intestinal alkalinity is lowest, and must therefore be administered when upper intestinal digestive activity is at a minimum, *i. e.*, a short time before meals. We believe that neglect of this very important consideration is responsible for many unsatisfactory responses to this form of therapy. Calcium gluconate is administered in doses of 60 grains, 3 to 4 times daily, $3\frac{1}{2}$ to 4 hours after meals. Patients are cautioned to avoid eating between meals. Parathyroid extract (parathormone) is injected intramuscularly, the average adult dose being 20 units. The injections are repeated at intervals of 48 to 72 hours, depending upon the severity of the symptoms.

Clinical Observations. Table 1 contains, in summary form, the pertinent observations made upon the first series of 13 patients, as reported in 1931, and their clinical condition at that time. Ten of the 13 were under observation at the time of the previous report. The subsequent course of these patients is summarized in Table 2. Two have died, 1 of pneumonia (C. T.) and 1 of carcinoma of the descending colon (J. H.); 2 were followed for an additional 2 years but have not been seen for the past 2 years; 6 are still under observation. Eight patients, therefore, have been observed for 2 to 6 years. Of this group, 5 have remained symptom-free for 2 to 6 years; (2, 2 years; 1, 3 years; 2, 6 years); 2 patients (J. E.B. and S.B.) have had remissions of relatively short duration at almost yearly intervals; in 1 case (R. S.) the disease has continued to progress.

The tendency to recurrence is a recognized feature of chronic ulcerative colitis, and it is difficult to determine when, if ever, recovery is complete. Although there may be freedom from all subjective and objective manifestations and a normal appearance

TABLE 1.—SUMMARY OF DATA PRESENTED IN 1931.

Patient.	Age.	Duration of symptoms.	Previous treatment.	Special features.	Duration of calcium treatment.	Period of observation.	Present appearance of mucosa.	Condition since treatment.
J. E. B.	35	8 mos.	Irrigations 3 mos.	6 weeks	30 mos.	Slight congestion	Well.
C. T.	48	8 mos.	Dietetic; sedatives	30 pounds loss in weight and nervous phenomena	8 weeks	24 mos.	Normal	Occasional mucus.
B. O. G.	26	10 yrs.	Appendicectomy in fifth year; irrigations	Frequent remissions, longest 4 months	8 weeks	22 mos.	Reddened and thickened	Symptom-free 14 months.
M. A.	41	4 yrs.	Sedative drugs	Lower rectum slow in healing	4 weeks; after 2 mos., 8 weeks	24 mos.	Normal 4 mos. after treatment ended	Tendency toward constipation.
E. d'A.	30	1 yr.	Irrigations; diet; sedatives	Abdominal pain marked	6 weeks	30 mos.	Slight congestion	Occasional mucus in stool.
S. B.	27	2 yrs.	Dietetic	Associated with nervous symptoms	4 weeks	24 mos.	Glazed, pale	Acute attack for 1 week a year later.
J. H.. . . .	54	4 mos.	None	7 weeks	12 mos.	Normal	Return of symptoms after 8 mos.
F. S.	45	4 yrs.	Irrigations	8 weeks	26 mos.	Normal	Occasional mucus.
H. S.	45	12 yrs.	Appendicectomy; normal saline irrigations	Symptom-free 3 yrs. after operation	4 weeks, then discontinued	Not traced	No bleeding ulcers; not entirely healed.	
F. E.	20	7 mos.	None	6 weeks	Not traced	Slightly edematous and granular.	
I. K.	58	3-4 wks.	Rectal instillations	7 weeks	13 mos.	Normal	Well.
R. S.	25	12 yrs.	Dietetic	Remissions 4 mos. yearly almost	3 mos.	10 mos.	No improvement	Bleeding only occasionally; frequency of stool persists.
J. S.	30	3 yrs.	None	1 mo.; discontinued	1 mo.; did not continue	No improvement.	

of the mucous membrane upon sigmoidoscopic examination, remissions sometimes occur after a lapse of years, at times apparently induced by a severe upper respiratory infection or other illness. Two remissions, each of about 2 months' duration, occurred in 1 patient (J. E. B.) while another (S. B.) had several remissions of 3 to 4 weeks' duration at almost yearly intervals; in both cases the response to treatment was comparatively prompt and entirely satisfactory.

TABLE 2.—FOLLOW-UP DATA IN 10 CASES PREVIOUSLY REPORTED AS SUMMARIZED IN TABLE 1.

Patient.	Period observation.	Relapse.	Response in relapse.	Present mucosal appearance.	Present condition.
J. E. B.	6 yrs.	10-1-32 (2 mo.) 11-1-31 (2 mo.)	Slow but complete	Slight congestion	Symptom-free 18 months.
C. T.	3 yrs.	Remained well 3 years; death—pneumonia.
B. O. G.	6 yrs.	10-1-31	Prompt	Atrophic changes	Well; gained 40 pounds
M. A.	4 yrs.	None for 2 yrs.	Normal	Not seen for 1 year.
E. d'A.	6 yrs.	None	Moderate congestion	Irritable colon, no ulceration or bleeding.
S. B.	6 yrs.	Yearly, early (2-4 wks.)	Prompt	Glazed pale	Irregular bowel function; occasional frequency.
J. H.	2 yrs.	8 mos. after discharge	Death—polyposis, carcinoma of colon.
F. S.	6 yrs.	None	Slight congestion	Frequent mucus, otherwise well.
I. K.	2 yrs.	Remained well 2 years, not seen since.
R. S.	5 yrs.	Progressively worse	Ileostomy October, 1932 no improvement	Progressive rectal stenosis and bleeding	Unimproved nephritis and anemia.

With the exception of Case R. S. (Table 1) the general condition of the patients in this group has been good, both weight and blood count having returned to normal. Some irregularity of bowel function persists in 2 instances (E. d'A. and S. B.). The former has had attacks of frequency of bowel movement lasting 1 to 3 days, while the latter passes an excessive quantity of mucus. In these patients, the mucous membrane of the bowel has appeared either slightly congested or pale and glazed. Similar changes were present in the bowel in 3 other cases without symptoms and no definite relationship could be demonstrated between the condition of the bowel mucosa and the symptoms exhibited by those patients with mild disturbances of bowel function. The bowel resumed an absolutely normal appearance in only 1 patient, who was, however, under observation for a shorter time than the remainder of this group. In Case R. S., a well-functioning ileostomy resulted in no

improvement in the condition of the colon, Roentgen ray showing extension of the ulcerative process into the ascending colon 1 year after operation. The mucous membrane of the rectum and sigmoid remained extensively ulcerated and friable, with frequent bloody and purulent discharge, and the patient has presented evidence of a progressively advancing nephritis during the past 2 years.

Observations have been made upon 16 additional patients over a period of from 6 months to 4 years. The pertinent data are presented in Table 3. The age incidence, which varied from 14 to 40 years, was as usual for this disease. The average duration of symptoms was 14 months. All presented fairly characteristic changes in the bowel mucosa. Proctoscopic material failed to reveal *E. histolytica* or other specific organisms, including that reported by Bargen. The period of calcium and parathyroid therapy averaged 7 weeks (3 weeks to 3½ months).

Eight of the 16 patients became entirely symptom-free within 3 to 12 weeks. Of these 8, 4 had short remissions (2 to 4 weeks) which responded promptly to treatment and all have been well for 6 months to 2 years, the bowel having resumed a practically normal appearance upon sigmoidoscopic examination. Of the 16 patients 7 were relieved of their severe symptoms and were restored to fairly good health, with a return of weight and blood count to normal, but with some degree of persistent disturbance of bowel function. Of the 7, 4 suffer with occasional abdominal distress, excessive flatulence and either constipation or increased frequency of bowel movement; they show no evidence of ulceration or bleeding but the mucosa remains somewhat edematous and congested. The other 3 have had persistent frequency of bowel movement, with semiformal stools, but their general condition has been quite satisfactory. Two of these patients were 14 years of age, and in both the condition was more resistant to treatment than in the other individuals in this series. The period of calcium therapy was also longer than in the case of the adults. When first seen, bowel symptoms were severe and both were markedly underweight, with a marked secondary anemia. Blood transfusions and other general measures were employed and, except for the increased frequency of stool, their condition is good at the present time.

One patient failed to respond satisfactorily to treatment (Case 14, L. J.). Bleeding invariably recurred after periods of subsidence of 2 to 3 weeks, and no appreciable improvement followed the institution of other forms of treatment. This patient, who had previously been in apparently good health, began to suffer from marked frequency of bowel movement following two severe emotional shocks in rapid succession. Bleeding was first noted 2 months later, and when first seen extensive superficial ulceration was present. The distressing emotional factors continued to operate and it seemed

that no definite improvement would occur in this case until these factors could be removed.

TABLE 3.—SUMMARY OF DATA IN NEW CASES.

Patient.	Age.	Duration	Special features.	Previous treatment.	Duration calcium treatment.	Period of observation.	Present mucosal appearance.	Condition since treatment.
1. E. P.	14	2 yrs.	Marked weight loss secondary anemia	General dietetic	2½ mos.	18 mos.	Congestion	Irregular bowel function, no bleeding.
2. R. C.	25	2 yrs.	Postpartum anemia leukopenia	General	1 mo. (1) 8 mo. interval (2) 4 mo.	3½ yrs.	Normal	1 remission (1 mo.), symptom-free 12 mos.
3. E. L.	31	7 mos.	Arthritis anemia	Removal focal infection, transfusion	4 wks.	3 yrs.	congestion	Occasional frequency.
4. S. S.	33	2 mos.	Severe abdominal pain, anemia	General transfusion	8 wks.	6 mos.	Edematous	Symptom-free, blood count near normal.
5. R. G.	50	2 yrs.	Remission 3 mos. after onset. Recurrence 1 yr. later	General	1 mo.	6 mos.	Congestion	Symptom-free.
6. R. K.	14	3 yrs.	Perirectal abscesses, fever, loss of weight	General antidiarrhea mixtures	3½ mos.	3 yrs.	Diffusely congested	2-3 semiformed stools daily, occasional blood, weight normal, condition good.
7. J. W.	49	2 yrs.	3-4 stools daily, slight bleeding	None	1 mo.	18 mos.	Normal	Occasional pain and soft stools, no bleeding.
8. M. C.	30	10 mos.	Marked anemia, vomiting	Dietetic transfusion	3 mos.	4 yrs.	Normal	Symptom-free.
9. C. M.	26	2½ yrs.	3-10 stools, slight bleeding	Bargen serum, vaccine, dietetic	3 wks.	16 mos.	Not examined recently	1 brief relapse after 1 yr., condition good.
10. J. C.	29	5 mos.	Marked anemia, constipation	None	3 wks.	3½ yrs.	Dry glazed	Symptom-free, blood count normal.
11. M. K.	25	6 mos.	Marked frequency anemia	General	9 wks.	1 yr.	Congestion, edema	No bleeding, 5-7 stools daily.
12. R. B.	39	18 mos.	Marked bleeding	Dietetic, local	5 wks.	18 mos.	Recurrence after 4 mos. Treated 4 wks., symptom-free 1 yr.
13. L. F.	26	5 mos.	Postpartum	Anti-diarrhea mixtures	5 wks.	2 yrs.	Congested granular	1 remission (2 wks.). Occasional symptom of irritable colon.
14. L. J.	36	5 mos.	Long constipation daily laxatives followed emotional upset	Dietetic, medicinal	3 mos.	10 mos.	Granular congested few ulcers	Periodic partial improvement, seldom symptom-free.
15. C. C.	28	6 mos.	Constipation and diarrhea 1 yr. before onset of bleeding	Thyroidectomy, dietetic	10 wks.	18 mos.	Dry glazed	Frequent constipation and flatulence.
16. D. C.	26	3 mos.	Appendectomy 2 mos. after onset, condition worse	Dietetic, medicinal	10 wks.	20 mos.	Congested	1 relapse (3 wks.) following acute respiratory infection.

Discussion. From a clinical standpoint, the favorable therapeutic response to calcium and parathyroid administration noted in the great majority of the cases included in the present report was characterized by rather prompt improvement in two outstanding features of the disease, namely, bleeding from the bowel and colonic spasm and hyperirritability. Cessation of bleeding, which was in most instances the earliest and most constant indication of improvement following the institution of this form of therapy, is, in our opinion, an important factor in bringing about healing of the ulcers. Of perhaps equal importance is the apparently beneficial influence of calcium therapy upon colonic hyperirritability which, with the associated spastic condition of the bowel, must inevitably interfere with healing. Marked reduction in pain and in frequency of stool was noted in several cases in which full doses of belladonna had been ineffectual. It is naturally impossible to state whether healing of the ulcerated areas is predominantly the cause or the effect of the diminished irritability and bleeding. It may be, as suggested in our first report,¹ that calcium favors the healing process directly, by improving the nutrition of the inflamed and edematous bowel wall.

Although the response to treatment was usually prompt in the majority of cases in which favorable results were obtained, definite improvement began in several patients only after parathyroid and calcium therapy had been continued for periods of 4 to 6 weeks, and an adequate response was obtained in 3 patients only after 3 months of continuous treatment. In no instance was any untoward effect observed. It is interesting to note that the response to treatment during relapse in individual cases was almost invariably identical with that observed at the primary institution of treatment. So far as could be determined, those cases in which improvement was prompt and marked differed in no essential respect, either clinically or in the appearance of the bowel, from those which showed no improvement.

Conclusions. 1. Nine patients with chronic ulcerative colitis have been observed for periods of 2 to 6 years after their original course of calcium and parathyroid therapy. Five have remained essentially symptom-free; brief remissions occurred in 2 instances which, however, responded promptly to the same form of treatment. One patient with nephritis and anemia is unimproved and 1 died of pneumonia after remaining well for 3 years.

2. Sixteen additional cases have been treated similarly and have been observed for periods of 6 months to 4 years. Eight became clinically well, 7 were relieved of their severe symptoms and were restored to fairly normal health, with some evidence of persisting colonic irritability, and 1 patient was not benefited.

3. Although the response to treatment is usually prompt, definite improvement occurred in 3 cases only after 3 months of continuous

calcium and parathyroid administration. Cessation of bleeding is the earliest and most constant indication of improvement in the majority of cases.

4. The rationale of calcium therapy in chronic ulcerative colitis is believed to rest upon the favorable influence of calcium upon the following existing conditions: *a*, Nutritional change in the tissues, with or without a disturbance of calcium partition; *b*, spasticity and hyperirritability of the colon; *c*, slow, capillary bleeding.

The calcium gluconate used was supplied through the courtesy of the Sandoz Chemical Company.

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DIABETIC COMA WITH EXTREME HYPERGLYCEMIA.

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OUR interest in this subject was aroused by a recent patient whose blood sugar was 1850 mg. and who recovered. Recovery in cases of diabetic coma with extreme hyperglycemia is not common, but the literature does contain a few reports.

Marble, Root and White¹ reported that 10 cases had been encountered at the George F. Baker Clinic with blood sugars of 1000 mg. or more, of which 6 recovered and 4 died. Curtis and Dixson² previously reported 1 case of this group which had a blood sugar of 1620 mg. and recovered. Kehr and Kocher³ reported a case with a blood sugar of 1028 mg.; Gray and Sansum,⁴ a case with a blood sugar of 1000 mg.; Shepardson and Anderson,⁵ a case with a blood sugar of 1090 mg.; and Foster,⁶ a case with a blood sugar of 1260 mg. All of these cases recovered.

Higher blood sugars have been reported in cases which died. Lawrence⁷ reported a case which he treated, in 1930, with a blood sugar of 2060 mg. 2 hours after 40 units of insulin had been given. Argy⁸ reported a case with a blood sugar of 1710 mg. without acetone in the urine; and Pitfield⁹ had a case with 1700 mg.

We are presenting the records of 16 cases of diabetic coma in

which the blood sugar was 1000 mg. or more at admission to the wards of the Metabolic Department, Philadelphia General Hospital.

TABLE 1.—CASES OF DIABETIC COMA IN WHICH THE BLOOD SUGAR WAS 1000 MG. OR ABOVE.

Case.	Name.	Age.	Sex.	Race	Date.	Admission.	Blood sugar (mg.).	CO ₂ .	Urea N.	Outcome.
1	T. J.	40?	M.	B.	11/23/25	First	1520	21	..	Died 3 hrs.; autopsy.
2	M. M.	58	F.	W.	4/ 2/26	First	1120	..	45	Recovered.
3	T. M.	27	M.	W.	1/12/27	Fifth	1484	11	..	Died 8 hrs.
4	E. T.	50	F.	B.	7/19/28	First	1060	8	30	Died 16 hrs.; autopsy.
5	H. H.	30	F.	B.	3/30/29	First	1080	11	21	Recovered.
6	G. M.	28	F.	B.	12/11/29	First	1030	12	50	Died 25 hrs.; autopsy.
7	J. J.	35	M.	B.	1/29/30	First	1500	24	..	Died 8 hrs.; autopsy.
8	H. H.	31	F.	B.	5/14/30	Second	1056	10	..	Died 6 hrs.; autopsy.
9	C. R.	46	F.	B.	6/12/31	First	1056	18	55	Recovered.
10	S. D.	20	F.	W.	9/11/31	Seventeenth	1000	16	..	Died at admission.
11	L. J.	53	F.	B.	6/10/34	First	1028	12	..	Died 2 hrs.; autopsy.
12	M. H.	54	F.	B.	10/ 5/34	First	1008	22	95	Died 59 hrs.; autopsy.
13	M. S.	40	F.	W.	10/ 9/34	Sixth	1000	7	20	Died 16 hrs.
14	N. D.	21	F.	B.	12/23/34	First	1850	13	95	Recovered.
15	F. C.	39	F.	B.	1/20/35	First	1024	15	63	Recovered.
16	S. P.	56	F.	W.	2/28/35	First	1470	10	42	Died 2 hrs.; autopsy.

These cases occurred among 3461 admission to this department up to March 1, 1935. Three of these cases (Nos. 2, 5 and 9) have been reported previously by Haines and Davis.¹⁰

Of the 16 patients, 5 recovered and 11 died; 13 were women and only 3 were men. There were no children. We were astonished to find that 11 were negroes. According to the 1930 census, negroes constituted 11.3% of the population of Philadelphia. Of all the patients admitted to the hospital, 28.5% are negroes, and of those admitted to the Metabolic Department, 20% are negroes.

Of these cases, 12 were previously unknown to this department. Cases 5 and 8 were the same individual. Three patients (Nos. 3, 10, 13) were chronic offenders. Patient 10 was admitted to the department 17 times in 3 years, twice with a CO₂ of 6, 8 times with CO₂ of 11 to 20, 5 times with CO₂ of 21 to 27, and twice with a normal CO₂.

Patient 12 had severe gangrene of a foot and leg. A thigh amputation was performed 19 hours after admission, at which time the blood sugar was 520, CO₂ 56, urea nitrogen 60. She died 40 hours after the operation.

Patient 16 had extensive gangrene of both feet.

We are reporting Patient 14 in detail, because we have not seen in this clinic, nor have we been able to find in the literature, a similar case of hyperglycemia with recovery.

Case Report. N. D., aged 21, colored female, was first admitted to the Philadelphia General Hospital, June 27, 1934, at which time she was delivered at term of a living female child. Four urine examinations were negative at this time for sugar. Because of a minor infection in the episiotomy wound, the patient was not discharged until July 20, 1934, at which time she and the baby were in good condition.

TABLE 2.—DETAILS OF COURSE AND TREATMENT OF CASE 14.

	Time.	Blood sugar.	Urea N.	CO ₂ .	Hemoglobin. W. B. C.	Blood pressure.	Insulin.	Saline.	Glucose, gm.	NaHCO ₃ , gr.	Acacia, gm.	Cholesterol.	Whole blood chlorid.	Blood sulphur.	Urine.
12/23/34	4:30 P.M.	1850	95	13	16.8	30/0	280	500	..	160	30	400 cc. Cath. 90 cc. 250 cc.
	7:00 P.M.	1550	..	13	12,700	82/30	200	2000	..	120	..	170	430	..	
	9:00 P.M.	1280	..	18	70/30	100	500	30	
	12:00 P.M.	896	..	32	74/30	80	2000	90	120	
12/24/34	3:00 A.M.	720	..	47	76/40	..	1500	500 cc. 700 cc. 750 cc. 950 cc.
	6:00 A.M.	610	..	48	13.1	84/42	460	..	
	8:00 A.M.	488	79	56	9,800	86/34	..	2000	30	
	10:00 A.M.	544	..	56	88/68	30	
	12:30 P.M.	360	..	54	90/64	20	250	50	500 cc. 700 cc. 750 cc. 950 cc.
	7:00 P.M.	268	..	61	90/64	
	12:00 P.M.	302	3	
	7:00 A.M.	266	33	57	
12/25/34	7:00 A.M.	159	
1/31/35*	7:00 A.M.	159	

* Diet: P., 60; F., 130; C., 140. Insulin: 10-0-0. Twenty-four-hour urine sugar, negative.

Following discharge she was well until December 9, 1934, when she became increasingly weak, until December 21, when she became delirious. She was admitted to this department, December 23. The patient was semi-conscious and extremely restless; temperature 96° F. (rectal), pulse imperceptible, respirations 36. The respirations were not typically Kussmaul. The physical examination were essentially negative, except for soft eyeballs, inaudible heart sounds and blood pressure of 30 systolic and 0 diastolic.

Blood studies at 4.30 P.M. showed blood sugar (Folin-Wu) 1850 mg. (checked), urea nitrogen 95 mg., CO₂ 13 vol. %. The progress and treatment can be followed best in Table 2. Sixteen hours after admission the patient was completely conscious and oriented. On December 25, 1934, the patient took a liquid diet of protein 60 grams, fat 130 grams and carbohydrate 140 grams.

Five days after admission her temperature rose and the left chest showed physical signs of lobar pneumonia. This was substantiated by roentgenogram. Her convalescence was slow, but uneventful, the temperature coming to normal on the 17th day. She was readily standardized on a diet of protein 60 grams, fat 130 grams, carbohydrate 140 grams and 10 units of insulin before breakfast.

Of interest in this patient was the exceptionally high initial blood sugar and the profound state of "medical shock" on admission. The response to treatment was rapid and continuous.

A total of 660 units of insulin, 6500 cc. of normal saline solution, 400 grains of sodium bicarbonate, 60 grams of acacia, 90 grams of glucose were given in 12 hours.

The plasma cholesterol 2½ hours after admission was 170 mg., of which 82 mg. (48%) was ester. The whole-blood chlorid, taken at the same time, was 430 mg. and the blood sulphur was 8 mg. Seven days later the plasma cholesterol was 112 mg., ester 43 mg. (38.4%), the sulphur 1.2 mg., and the whole-blood chlorid 520 mg.

The Kahn reaction was negative.

All blood analyses during this coma were done by Mr. T. V. Letonoff, Chief Chemist of this clinic.

Summary. Sixteen cases of diabetic coma are reported which had blood sugars of 1000 mg. or above at admission to the hospital. One patient had a blood sugar of 1850 mg., the highest on record in which recovery occurred.

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THE METABOLISM OF GALACTOSE.*

III. THE INFLUENCE OF DISTURBED ENDOCRINE FUNCTION.

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IN a series of earlier papers,¹ the author and his associates have presented the results of investigation on the influence of a variety of agencies upon the capacity of the human organism to utilize galactose.† That disturbed function of the several endocrine glands exercises a profound influence on carbohydrate metabolism has long been recognized. An extensive literature on the topic exists, and includes the description of numerous efforts to utilize this fact for the diagnosis of disorders of the ductless glands. Equally, it has been known that disturbances in sugar metabolism may arise from an even larger number of non-endocrine causes, and these, too, have received due investigation and report. The determination

* This and the following paper had been completely prepared for publication before Dr. Rowe's death, in December, 1934.

† An earlier survey of the present topic was accepted and held for publication by a journal which has since been discontinued. As interest in the metabolism of this sugar has been recently reawakened, the present material has been collated, incorporating certain of the newer ideas and drawing on a more extensive material.

of the so-called carbohydrate tolerance as evidence of disease constitutes a frequently advocated diagnostic procedure and one the validity of which is denied with equal frequency. The conditions of application of the test and the interpretation of results are almost as numerous as the articles describing them. One principal cause of conflicting reports is a seeming failure to recognize that the application of the test leads to the measurement of a single end result common to a wide variety of causes. Further, there may coëxist in the single organism two or more agencies, each capable of influencing sugar utilization, producing reinforcement or antagonism, and that the tolerance as measured is the algebraic sum of these several factors. The crucial experiments of Houssay² and Barnes³ leave no doubt as to the validity of this fact so far as ductless glandular agencies are concerned; these and other factors will be considered in the body of this paper. Failure to make due allowance for the carbohydrate paradox (Allen⁴) and the limitation of the quantitative significance of the blood-sugar curve are among the other factors which have produced completely contradictory interpretations. For the above and similar valid reasons, no review of the literature will be presented; citations as they occur are solely expository to the text, offering the interested reader access to additional detail.

For purposes of this study, we have adopted the original Hofmeister⁵ technique, *i. e.*, the use of a series of graded test meals with the production of a transitory galactosuria as the index of an exceeded limit of utilization. The method of application of the test has been discussed at length in the earlier papers¹ and need not be repeated here.

The cases utilized for this study had all received a comprehensive clinical and laboratory study during a period of not less than 7 days' hospitalization,⁶ and the diagnoses were derived from the integration of all of these resulting evidences, each interpreted in terms of all other pertinent data. Effort was made to ascertain all departures from the physical normal presented by the individual with a just recognition of the possible misleading influence of unrecognized superimposed effects.

The cases have been selected, so far as possible, to eliminate those complications which could and do independently influence carbohydrate metabolism. The results from such superimposed effects, in those few cases presenting them, and which for a variety of reasons have been included in the series, will be discussed at the appropriate point in the text.

A series of 1000 cases has been selected for this survey, comprising patients with the various types of disturbed function of the pituitary and thyroid, supplemented by series of ovarian and pancreatic failure, and a small group with hypofunction of the adrenals. The partition among the several etiologic entities is given in Table 1.

TABLE 1.—COMPOSITION OF GROUP.

Gland.	Function level.	Number.
Pituitary	Hyperfunction (+)	10
	Dysfunction (±)	300
	Hypofunction (—)	150
Thyroid	Hyperfunction (+)	25
	Dysfunction (±)	75
	Hypofunction (—)	150
Ovary*	Hypofunction (—)	250
Pancreas	Hypofunction (—)	30
Adrenal	Hypofunction (—)	10
		<hr/>
		1000

* Functional failure, 225; castrates, 25.

A few words as to the basis of selection is called for.

The pituitary, thyroid and ovarian groups show a numerical relationship which is approximately that of their appearance in the diagnostic clinic. That the figures are influenced by this origin is certain, and as a statistic cannot be interpreted in terms of usual frequency of incidence in the community. Hyperpituitarism and hyperthyroidism find but scant representation, largely because these conditions in an established state do not call for an elaborate diagnostic survey and are referred primarily for treatment. The figures for the dysfunctional and hypofunctional stadia are more nearly characteristic, since their somatic evidences are less distinctive and as a medical rather than a surgical approach is the therapy of election. Likewise, the diabetics are cases for treatment rather than for an elaborate diagnostic approach; the adrenal cases do no more than reflect the rarity of established adrenal failure. The testicle has been omitted as the adult male castrate presents a normal sugar metabolism, and we are lacking objective evidence of any significant endocrine influence of these glands in the adult human.⁷ The parathyroids have also been excluded, in largest part from a dearth of suitable material. The statement has been occasionally—and somewhat loosely—made that parathyroid failure lowers the sugar tolerance. This seemingly derives from animal experiments; Falta,⁸ who reports this phenomenon with parathyroidectomized dogs, could not duplicate it in cases of idiopathic tetany in man. Erdheim,⁹ using galactose (40 gm.) and blood-sugar curves, could find no lowering of tolerance in idiopathic tetany; on the other hand, he interprets his results to indicate a probable moderate increase. Our few cases of osteitis fibrosa cystica have presented disturbing complications which have precluded the certain estimation of the parathyroid influence.

Before discussing the numerical data, certain terms must be defined for the sake of clarity. Hypofunction is that picture produced by ablation of the gland or by its known definitely depressed hormone production. Hyperfunction, naturally the antithesis so far as hormone production is concerned, is recognized in this series

only in the thyroid and pituitary groups. While all aberrant activities are dysfunctions, this latter caption has been reserved, for classificatory purposes, to those conditions in which evidences are presented simultaneously in the same subject of both overactivity and underactivity. In the case of the thyroid, one is certainly dealing with a transitional state sometimes evoked by surgery, more frequently, in this series at least, by spontaneous sequential functional depression. With the pituitary, yet other permutational elements enter in as there are two well-differentiated lobes; the pars intermedia is believed by many to constitute a third functional entity, and the infundibulum, remotely, may constitute a fourth. Dysfunction, then, of this composite gland may include any of the rather numerous possibilities of inequality of functional level, together with a true transitional status. The usual formula of objective evidences includes, among others, a lowered basal rate and sugar tolerance, although the opposite condition may obtain. We have been privileged through the years to observe a small number of cases which, starting at an initial level of hormonal overproduction, have escaped surgery, and through the years have declined gradually to a terminal hypofunction. As early as 1911, Cushing and his associates¹⁰ reported this sequence in the carbohydrate metabolism of a series of pituitary cases.

Certain general data, either defining the individuals composing the group or bearing directly on their general sugar metabolism, have been collected.

TABLE 2.—PITUITARY.

Datum.	Function.			Average or total.
	+	=	-	
Male	4	85	41	130
Female	6	215	109	330
Age, low, yrs.	19	4	7	
high, yrs.	63	68	71	
average, yrs.	38.8	31.8	30.6	31.5
Glycosuria, % +	50.0	17.0	0	
Blood sugar, low, mg.	86	72	72	
high, mg.	100	115	119	
average, mg.	93	91	94	92

Broadly speaking, the females outnumber the males in a proportion of 5 to 2. The ages show a wide range between individuals, but a nearly constant average in the two groups of appreciable proportions. Half of the hyperfunctional and none of the hypofunctional group show glycosuria, with an intermediate value for the group of dysfunctional cases. The blood-sugar values show nothing remarkable other than the fact that so many individuals with normal blood sugars demonstrate a slight but definite glycosuria. This is certainly a reflection of a disturbed carbohydrate metabolism which cannot be solved by the convenient postulate of a "renal glycosuria," and which leaves the fundamental question still in abeyance.

TABLE 3.—THYROID.

Datum.	Function.			Average or total.
	+	±	-	
Male	9	11	50	70
Female	16	64	100	180
Age, low, yrs.	6	8	5	
high, yrs.	58	66	71	
average, yrs.	36.4	27.4	24.4	26.5
Glycosuria, % +	28.0	12.0	4.0*	
Blood sugar, low, mg.	80	73	71	
high, mg.	111	120	118	
average, mg.	92	96	92	93

* Four cases with no demonstrable complication, 1 psychosis and 1 gonorrhea.

The sex division in the thyroid group shows almost identically the same average as did the pituitary. There is a definitely lesser uniformity throughout the three functional subgroups with the dysfunctional series showing but 1 male in 7. The explanation is not forthcoming. The ages show a decline as one progresses toward lessened function; this is undoubtedly due in part to the relatively large number of children studied who presented a thyroid failure dating from early childhood.

Glycosuria in the overactive group is but half as frequently recorded as in the equivalent pituitary moiety. The dysfunctional figures more nearly concur with those of the hypophysis, and even the hypofunctional fraction shows a modest number of patients with glycosuria. Two of these had complications which were possibly the causal agents; the other 4 did not, and it seems probable that they were transitional cases, the glycosuria being the sole persistent residuum of their earlier hyperactive state. The blood sugars, as in the case of the pituitary, show nothing remarkable, all falling within the limits of the conventional normal zone. From the figures as quoted, it is permissible to infer that the influence of the thyroid on carbohydrate metabolism, while considerable and operating in the same sense, is certainly less than that of the pituitary.

As the other endocrine structures under discussion present but one level of functional activity, their data can be combined in Table 4. Allowance is made in the diabetic group for those presenting a picture modified by insulin therapy.

TABLE 4.—OTHER ENDOCRINE GLANDS.

Datum.	Ovary.	Pancreas.		Adrenal.
		Insulin.	Untreated.	
Male	0	10		3
Female	250	20		7
Age, low, yrs.	14	11		22
high, yrs.	68	70		61
average, yrs.	34.7	50.3		35.7
Glycosuria, % +	23.0	75	100	40.0
Blood sugar, low, mg.	75	81	158	74
high, mg.	118	173	334	85
average, mg.	94	118	234	79

All of the ovarian cases had matured; the series average falls but slightly above that of the pituitary group. One-fourth of the series showed glycosuria, while the blood-sugar values were entirely normal. It may be said in passing that the higher levels of blood sugar recorded throughout the first three major groups not improbably reflect a nervous response to venipuncture; this is certainly the case with a number of the oversensitized individuals with ovarian failure. With the pancreatic group, the sex proportion approximates that of the pituitary and thyroid series, and the same is true for our few adrenal cases. The diabetics are distinctly older as a group, although the age scatter is substantially that of the other series. The youngest adrenal case was 22 years; the average age falls in the middle of the fourth decade.

As was to be anticipated, glycosuria of a marked degree characterized the diabetics, but a few insulinized patients being sugar free. A high incidence (40%) was also found in the adrenal group. As was noted a number of years ago,¹¹ the earlier reports of an increased tolerance in Addison's disease in large measure derived from an erroneous interpretation of animal experiments and the general response to suprarenin. The two groups of pancreatic cases exhibit blood-sugar levels determined by their relative therapeutic status. The adrenal blood sugars show a trend toward that hypoglycemic level which is now generally recognized as characteristic of the condition.

To summarize briefly, glycosuria appears through the entire series with significant frequency with the exception of the pituitary failures and, in nearly equal measure, those of the thyroid. Blood sugars are normal except in diabetes where the hyperglycemia is pathognomonic, and in the adrenal group where the converse is almost equally typical.

Before reporting the results of the galactose testing, a few words as to standards are essential. While the normal healthy male seemingly responds to a dose of 30 gm. irrespective of age, the female shows a fluctuation seemingly intrinsic in her several levels of sexual maturity and activity. While the question has been discussed at length in the earlier papers, a brief review may be permissible for purposes of later orientation. The normal healthy prepuberal child responds to 20 gm. With the onset of menstruation, the level rises and in the course of the first year usually attains the adult standard of 40 gm. Menstruation and pregnancy tend to lower this adult level, the latter ultimately to the prepuberal standard of 20 gm., followed by gradual recovery to the adult plane after delivery. Castration likewise, after a period of adjustment, will produce a consistent prepuberal tolerance (v.i.). The writer has suggested in this a possible mammary influence and has offered certain documentation to support this thesis. Certainly in the adult female, free from complications which might affect sugar

metabolism, removal of the breasts drops the galactose tolerance from 40 to 20 gm. An interesting, indirect support is found further in the observation (unpublished data) that the adult tolerance for levulose is unaffected by ablation of the mammary glands in the human female.

Reverting to the definition of standards, the menopause seemingly produces some degree of retrogression in galactose tolerance, but without the uniformity that characterizes the other stadia. About two-thirds of the postmenopausal women respond to 30 gm.; the remainder retain the 40-gm. level of the normal adult.

It should perhaps be noted that the 10-gm. intervals mentioned in the preceding discussion do not imply abrupt transitions, but represent the conventional levels used in applying the test.

With the female standards dependent upon the levels of sexual activity, tolerance variations throughout the series can be equated only by expressing them in relative terms of departure from that normal which is appropriate to the individual. The same impediment does not exist with the male, but for purposes of uniformity in reporting, the same convention is adopted. The postmenopausal female introduces a difficulty in that seemingly normal individuals respond severally to both 30 and 40 gm. As a partial solution to the question, both of these levels are reported as normal (deviation \pm %) in the subsequent tables, and departures from these two levels are calculated on the basis of a mean postmenopausal level of 35 gm. The possible arithmetical errors introduced by the adoption of this convention are of minor magnitude, and with the small percentile representation of the cases requiring its use, the data are readily absorbed into averages which are no more than a first approximation. Further, an analysis of these postmenopausal cases constitutes a portion of this report, the data demonstrating the warrant of the convention adopted.

Turning now to the actual results of the tolerance testing, the data from the pituitary series have been collected in Table 5.

TABLE 5.—GALACTOSE TOLERANCE. PITUITARY.

Tolerance.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
High	-25	± 0	+350
Low	-87	-87	± 0
Above normal	0	0	98
Av. deviation	—	—	+73
Normal	0	3.7	2
Below normal	100	96.3	0
Av. deviation	-58	-51	—
Group deviation	-58	-49	+71

As will be seen, all of the hyperfunctional cases show a depressed tolerance, with an average deviation reaching the significant amount of -58%. In the large dysfunctional series, a few presented normal tolerances, but the great majority exhibited a depression of

the capacity of utilization for galactose, which in many cases, was of very marked degree. Fifteen of the earlier cases responded to a test meal of 5 gm.; in the more recent applications of the test, in the interest of economy of time for the patient, 10 gm. has been the smallest dose exhibited. All of these cases showed a definite lowering of the respiratory metabolism from normal standards.

With pituitary failure, there is a complete change in the sign of the departure from normal tolerance, and the deviations are even more pronounced than in the other two categories. It must not be forgotten, however, that there is a definite arithmetical limit to depressed values which does not operate in the zone of increased tolerance. Only 2% of this group showed a normal level, none were below and the average departure for the group, the considerable amount of +71%. However and through what agencies the effect be mediated, there can be no question but that the pituitary exercises a profound influence on sugar metabolism. Further, there is no other recorded agent which will produce the massive increases in tolerance which are characteristic of pituitary failure.

Leaving the hypophysis for the moment, the data from the thyroid series present:

TABLE 6.—GALACTOSE TOLERANCE. THYROID.

Tolerance.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
High	±0	±0	+100
Low	-75	-75	±0
Above normal	0	0	12.0
Av. deviation	—	—	+43
Normal	4.0	33.3	88.0
Below normal	96.0	66.7	0
Av. deviation	-60	-33	—
Group deviation	-58	-22	+5

Uniform with the pituitary in sense and direction, the hyperthyroid group shows no case with augmented tolerance. One patient was normal, and the remainder all exhibited varying degrees of depression. The group average fortuitously is identical with that of the equivalent pituitary subseries. The composing members were all definitely toxic, and transitional types (with the possible single exception) have been excluded. The clinical and laboratory pictures were typical; so far as is known, all of the cases in this series were operated upon subsequent to the study, but we have not complete data as many came from a distance and returned to their homes on completion of the diagnostic survey.

The dysfunctional moiety equally show no cases with increased tolerance, but one-third were normal, and the average depression of the utilization capacity of the group is of very modest proportions. Many of these were cases examined after operation and presented the characteristic irregularities in rapidity of the decline of objective evidences toward a normal or terminal hypofunctional level.

The established thyroid failures show a slight upward tendency of the tolerance which in isolated cases may assume really significant proportions (+100%). In the main, however, the effect on the carbohydrate metabolism is not marked, and 88% of the entire group yielded normal tests. If the degree of depression of the basal rate may be taken as a rough index of the lowering of glandular activity, the report of a single case in the series may be quoted in support. The patient was a man in his early sixties, with a long-standing and severe myxedema, and a basal rate 60% below his predicted normal. The blood and urine pictures gave evidence of definitely lowered renal permeability. He was positive with 50 gm. of sugar, or a deviation of +67%. The case with the tolerance increase of +100% reported in Table 6 was also an aged person with severe myxedema and renal impairment. As was noted above, the evidence indicates that the thyroid exercises a considerable influence on sugar metabolism in the same sense as does the pituitary but falling far short in degree of the effect of the latter. Some of the more recent work on intermediating hormonal influences between these two incretory structures may hold suggestions of an underlying mechanism. Discussion of these highly interesting matters, however, can find no place in the present statement.

In presenting the material from the examinations with the remaining endocrine groups, for initial presentation no difference is made between the ovarian failures of functional and those of surgical origin. True, it is known that removal of the sex glands in woman lowers her galactose tolerance to the prepuberal level, and that thus 20 gm. is her normal tolerance. She is an abnormal individual, however, and our primary effort is to ascertain the influence of abnormalities upon the sugar levels which characterize the normal, intact, adult female. The castrate group will have brief individual notice later in the text.

TABLE 7.—GALACTOSE TOLERANCE. OTHER ENDOCRINE GLANDS.
(HYPOFUNCTION.)

Tolerance.	Ovary, per cent.	Pancreas, per cent.	Adrenal, per cent.
High	±0	±0	-25
Low	-87	-75	-87
Above normal	0	0	0
Av. deviation	—	—	—
Normal	2.8	13.3	0
Below normal	97.2	86.7	100
Av. deviation	-47	-55	-62
Group deviation	-45	-48	-62

Here, in opposition to the two glands previously discussed, lowered functional activity determines a depression in tolerance of wholly significant proportions and operating certainly in 97% of the group of ovarian failures.

Lowered tolerance is to be anticipated with the diabetics, and

the present data offer no decided negation to the general trend. It is to be noted, however, that 13% show normal tolerances for galactose, and these are all in the untreated group. Further, the insulin influence in this small series is seemingly not a serious factor in determining the individual levels. Twelve cases were under insulin therapy, and their average deviation was -53% as against that of the 18 untreated cases which was -45% . Several explanations at once suggest themselves, the first and most probable being that the two groups are too small for the arithmetical values to have any precise significance. It might be argued further that the more severe cases were those under therapy, but an analysis of the case records fails to yield an unqualified support to this explanation. Several recent investigators^{12,13} have reported that insulin has no effect on the utilization of galactose (direct effect would be implied here), and our present small series certainly presents results that are not inharmonious with this report. There is, further, a recent literature, in part advocating the use of galactose by the diabetic, and in part denying its utility. Without entering the controversy, it may be said that the present figures offer some slight support to the first contention, as the utilization shown here is as good, or better, than in a number of the other endocrine conditions here reported. Too sweeping an inference should be avoided, (1) because of the small number of cases, and (2), since the mechanisms involved are patently different, the diabetics being the only cases exhibiting hyperglycemia.

The adrenal cases show an unvarying depression of galactose tolerance and one of the same order of magnitude as the extreme conditions of overactivity in thyroid and pituitary. The findings here are diametrically at odds with the usual statement concerning adrenal influence on sugar tolerance. There is a voluminous literature in this field, and practically all writers seem to concur in the opinion that adrenal failure produces an increase in the tolerance. The great majority of the studies, from which this opinion derives, are based upon the influence of suprarenin injections on the level of blood sugar, or less frequently on the production of glycosuria, procedures outside the range of this discussion. Of the very few studies which are comparable to the present investigation, Eppinger, Falta and Rüdinger¹⁴ state that they found a very high tolerance for sugar in 3 cases of Addison's disease, while numerous writers have reported the low blood-sugar curves which are considered indicative of an increased assimilation limit. A single exception is in a recent paper from Porges and Adlersberg,¹⁵ in which they report marked transitory hyperglycemia in Addison's disease after glucose feeding, a finding suggesting, though not certainly defining, a lowered utilization capacity.

In contradiction to this mass of opinion, all the cases in this series showed a depressed tolerance for galactose. Question as to

diagnosis is answered by the fact that in the typical cases, primary adrenal involvement was verified at autopsy. Kidney lesions seem to be the almost invariable complement of adrenal disease. The contradictory results of the other observers already cited may be due to lessened kidney permeability, possibly to the fact that galactose was not the sugar used, or possibly to other and unknown causes. The frequently observed hypoglycemia of adrenal failure has been confirmed in the present group. This might influence the so-called tolerance if determined solely by the character of blood-sugar curves without observation of the urine changes. As before stated, sugar anomalies produced by epinephrin injection fall outside the scope of the present discussion, as presumably they include a mechanism differentiated from that operated by the oral administration of sugar.

There remain yet a few additional matters which must be touched upon briefly. In the opening portion of this paper, comment was passed upon the well-known fact that a variety of agencies, not directly associated with ductless glandular activity, play definite parts in influencing sugar metabolism. Further, it was noted that, in largest measure, endocrine cases presenting such complications had been excluded from the present study series. Finally, attention was called to the demonstrable fact that where two such agencies operate in the same individual, the observed end result is an effect presenting the algebraic summation of their several influences. To illustrate these points and to touch upon other matters as well, two groups have been selected, one, a series of 25 castrates from within the body of the study group, the other, an appended series of 50 cases of thyroid failure complicated by hepatic dysfunction. The association presented in the second group is of fairly common occurrence and has already been described.¹⁶ Turning first to the castrates, it may again be noted that removal of the ovaries ultimately lowers the galactose tolerance to the prepuberal level of 20 gm. Time is necessary for readjustment, and the terminal condition does not appear at once. In a brief series now being studied in another connection (unpublished data), all of the composing members of which had been castrated less than three weeks before the study, 4 gave a positive response to 30, 3 to 20 and 2 to 10 gm. of galactose. One of the 2 with the low (10-gm.) tolerance had had a dermoid cyst in addition to a uterine malignancy, the other a chronic oöphoritis of long standing. Both of these influences could complicate the picture. Turning to Table 8, we find that 4 of the group had tolerances 10 gm. above that conditioned directly by their ovarian status. They were all aged women, castrated many years previously, and all had objective evidences of an established nephritis with a lowering of renal permeability. Four others in the group showed abnormally low tolerances, and all of these were syphilitic, a condition well known to influence the

carbohydrate metabolism. The uncomplicated cases all were in harmony with prediction; the 4 luetics demonstrate the effect of a superimposed reinforcing influence. The status of the 4 high cases is by no means so certain. A mechanical (physicochemical) impedance may have been, but was not certainly, the cause. It is a fact, however, that in the thousands of cases which have been tested with this sugar, there is concrete evidence pointing to a renal influence on tolerance. On the other hand, all the Addisonians have very real renal impairment and, as noted, all present significantly lowered tolerances. The facts are reported as they have been found; the correct explanation of them is not so surely forthcoming.

TABLE 8.—GALACTOSE TOLERANCE. CASTRATES (25).

Tolerance dose, gm.	Number.	Deviation, per cent.	Comment.
30	4	+50	Advanced nephritics.
20	17	±0	Uncomplicated.
10	2	-50	Syphilis.
5	2	-75	Syphilis.

In the second group showing a significant complication, the evidences are simpler and more concordant. It will be remembered that thyroid failure either raised the tolerance or failed to modify its normal level.

In the present series of thyroid failure complicated by various forms of hepatic dysfunction—all carefully substantiated by a variety of objective approaches—there were 10 males and 40 females. The ages ran from 12 to 70 years, with an average of 35.7, or definitely older than the uncomplicated group. But 2% showed glycosuria, and the blood-sugar data were rigorously normal (73 mg. and 114 mg. the extreme values) with an average of 90 mg. The galactose data are given in Table 9:

TABLE 9.—GALACTOSE TOLERANCE. THYROID FAILURE AND HEPATIC DYSFUNCTION.

Tolerance.	Number or average, per cent.
Normal	2
Below normal	98
Av. deviation	-55
Group deviation	-54

Of the series, 98% showed a depressed tolerance, and the average is at a level comparing favorably with the endocrine agencies which produce the most marked depression. Here the relatively slight upward trend of the thyroid failure is more than overbalanced by the more powerful depressing influence of the liver disturbances. With the exception of the liver,¹⁻⁷ all of the non-glandular conditions tend uniformly to produce a lowering of sugar utilization. Their principal effect then would be manifest in those incretory

states usually characterized by augmented tolerances, in other words, failures of the thyroid and the pituitary glands. The few cases from these categories presenting significant complication are collected in Table 10.

TABLE 10.—INFLUENCE OF COMPLICATIONS.

Gland and function.	Complication.	Number.	Average deviation, per cent.	Group deviation, per cent.
Pituitary hypofunction	Tumor	3	+128	+83
	Epilepsy	3	+78	
	Central neural lesion	4	+76	
	Gall bladder	4	+61	
Thyroid hypofunction	Central neural lesion	3	±0	±0
	Syphilis	2	±0	

The tumor cases are included here on the implication that their presence might increase intracranial pressure, and this in turn be productive of influence on other brain tissues. Actually, no such evidence is here forthcoming, and the 6 intrasellar tumor cases in the dysfunctional group are potentially supporting with an average depression of but -31%. The other figures speak for themselves, with the exception of the 2 thyroid cases with lues. They were both advanced in years, both had chronic interstitial nephritis, and with both the syphilis had been vigorously treated with seemingly a real measure of success.

Those cases in the total series may be briefly reviewed which exhibited normal tolerances in the demonstrated presence of conditions which would be usually assumed to produce abnormality. For purposes of completeness and to emphasize intrinsic differences, the complete thyroid data are also included.

TABLE 11.—GALACTOSE TOLERANCE. ANALYSIS OF NORMAL TOLERANCE.

Gland and function.	Total.	Menopause.	Remainder.
Pituitary: Dysfunction	11	7	{ Tumor, 1. Head trauma, 3.
Hypofunction	3	2	
Thyroid: Hyperfunction	1	1	Tumor, 1.
Dysfunction	25	0	0
Hypofunction	132	28	Uncomp., 25.
Ovary: Hypofunction	7	7	Uncomp., 101
Pancreas: Hypofunction	4	3	0
			Liver, 1.

As was noted earlier in the text, the postmenopausal cases introduce a minor complication with a double standard for normal performance. If, for example, 30 gm. were the true level, then all of the 40-gm. cases would show a slight increase (+33%). Equally, were 40 gm. the correct standard, the 30-gm. cases would present

a modest depression of -25% . The convention adopted of reporting both of these groups as normal makes possible the subclassification that is shown in Table 12. Further, the few remaining cases (exclusive of the thyroid series) show complications to which may be traced their abnormal normality.

To complete the survey of the postmenopausal factor, all of the pertinent data have been collected in Table 12.

TABLE 12.—GALACTOSE TOLERANCE. POSTMENOPAUSAL CASES.

Gland and function.	Positive.		Increased or diminished.	Total.
	40 gm.	30 gm.		
Pituitary: Hyperfunction	0	0	1 Dim.	1
Dysfunction	2	5	22 Dim.	29
Hypofunction	2	0	12 Inc.	14
Thyroid: Hyperfunction	0	1	3 Dim.	4
Dysfunction	0	0	0	0
Hypofunction	9	19	1 Inc.	29
Ovary: Hypofunction	0	7	19 Dim.	26
Pancreas: Hypofunction	0	3	8 Dim.	11
Adrenal: Hypofunction	0	0	0	0
Totals	13	35	66	114

Of the total of 114 postmenopausal cases, 66 show deviations which are wholly consistent with their demonstrated glandular status, and the uncertainty of the standard can affect only the numerical expression of their deviation and that in but non-significant amount. Of the remaining 48 cases, 28 fall in the hypothyroid group where a normal tolerance is the usual finding. There remains, then, only 20 cases— 2% of the series—in which the postmenopausal uncertainty could produce minor arithmetical variation. Patently, the effect is negligible. In view of the running comment throughout the body of the paper, further discussion is unnecessary, and the results can be compactly summarized in tabular form.

TABLE 13.—SUMMARY OF AVERAGE DEVIATIONS.

Gland.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
Pituitary	-58	-49	+71
Thyroid	-58	-22	+5
Ovary	—	—	-45
Pancreas	—	—	-48
Adrenal	—	—	-62

In considering the numerical values, it must be emphasized that they are only rough indices showing direction with certainty, but amounts of deviation only as an order of magnitude. The 10-gm. stadia of the test, the inclusion of all degrees of severity of involvement within the single group from which the average deviation is reported preclude the attachment of deep significance to small percentile differences.

Adrenal failure, with pituitary and thyroid hyperfunction, constitute one group, pituitary dysfunction, diabetes and ovarian failure a second, while severally, thyroid dysfunction, thyroid failure and pituitary failure forms each an independent gradation.

The author expresses his deep appreciation both to the subjects of this investigation and, more especially, to his colleagues and associates who have contributed the vast amount of factual evidences upon which the study is based and of which the galactose testing forms but a very small part.

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THE METABOLISM OF GALACTOSE.

VII. THE INFLUENCE ON TOLERANCE OF COEXISTING ENDOCRINOPATHIES.

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IN a recent paper¹ dealing with the influence of individual endocrine dysfunctions on the utilization capacity of the organism for galactose, note was made of a possible disturbing effect upon the expected tolerance through a coëxistent non-endocrine condition also influencing sugar metabolism. As illustration, data were presented from a series of patients with both thyroid failure and hepatic dysfunction in which, almost without exception, the depressing influence of the liver disorder overweighed the modest augmenting tendency of the lowered incretory function. It is reasonable to assume that where two or more agencies are operating in the same organism, the resultant will be the algebraic summation of the several influences, each expressed in its degree and direction. Houssay's pioneer work,² supplemented by the confirmatory data from more recent studies and other sources, leaves no doubt that such a condition operates when two specific endocrine glands are in question, the depressing influence of pancreatectomy balancing the augmenting effect of ablation of the pituitary.

While the so-called pluriglandular syndrome, in the older conventional use of the term, is seemingly the rarest of occurrences, yet in a long series of individuals with endocrine involvement occasionally a case presents in which the malfunction of two ductless glands is seemingly coëxistent. Even here there may be a reasonable question if one of the two was not the primary focus and the involvement of the second no more than one feature of a general derangement which in time may influence both other incretory and non-incretory structures alike. Waiving further discussion of this still controversial topic, it remains a fact that whether the aberrant functions be coincident or sequential in their genesis, at rare intervals an individual is studied who seemingly presents such a status. A more productive source of material lies in the larger group of patients who present a technical pluriglandularity in that a dysfunctional or hypofunctional condition of surgical origin of one gland is superimposed upon a hormonal abnormality of a second. Drawing upon both types of material, it has seemed interesting to ascertain how far the predicate of opposing or reinforcing effects

can be substantiated by direct observation. The present paper deals with such a survey.

In the earlier communication already cited, the analysis of 1000 carefully studied cases gave certain criteria of the several influences on tolerance, both as to direction and roughly as to amount. Hyperfunctional and hypofunctional states are largely the antithesis of each other and require no detailed description. The term dysfunctional has been reserved in this discussion for those conditions where the gland is in a state of transition from one functional level to another or where, as in the case of hypophysis, two or more differentiated tissues constituting a single gland offer a variety of permutational possibilities. The results of the initial study may be abstracted in tabular form, dealing only with the structures which are involved in the present study.

TABLE 1.—AVERAGE DEVIATIONS OF GALACTOSE TOLERANCE.

Gland.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
Pituitary	-58	-49	+71
Thyroid	-58	-22	+ 5
Ovary	-45
Pancreas	-48

But little additional comment need be made. The differences of degree and direction are obvious. Emphasis should be laid on the fact that too great significance must not attach to the actual numerical values. These are no more than averages, drawn from groups of patients whose glandular disturbances range from mild to severe. As this same limitation obtains throughout the several groups, some slight quantitative meaning is inherent in the several magnitudes; they are to be regarded, however, as tendential rather than definitive.

The omissions in the table have already been discussed in the previous paper and elsewhere. The technique of the application of the Hofmeister³ test, the establishment of normal criteria and other pertinent details have all been previously presented.⁴

The present series is confined to the female sex and all of the subjects had matured. The adult female tolerance level of 40 gm. applies to all of the group except those few individuals who had passed the natural climacteric. With the cases falling in this category, and following the previous convention, response to either 30 or 40 gm. is recorded as normal ($\pm 0\%$), and deviations above or below these levels are calculated from the mean value of 35 gm. The warrant of these conventions has been documented in the previous paper.¹

Turning now to the present group, the cases composing it can be presented in tabular form:

TABLE 2.—COMPOSITION OF GROUP.

Pituitary.	Thyroid.	Ovary.	Pancreas.	Number.		
				Surgi- cal.	Func- tional.	Total.
Dysfunction	Dysfunction	3	3	6
Hypofunction	Hypofunction	0	2	2
Hypofunction	...	Hypofunction	...	11	0	11
Dysfunction	...	Hypofunction	...	5	0	5
...	Hyperfunction	Hypofunction	...	3	0	3
...	Dysfunction	Hypofunction	...	7	0	7
...	Hypofunction	Hypofunction	...	7	0	7
Dysfunction	Hypofunction	0	4	4
...	...	Hypofunction	Hypofunction	2	0	2
Totals				38	9	47

It is perhaps apposite to note that all of these patients had been hospitalized for periods of not less than a week—many of them for appreciably longer intervals—and that each had received exhaustive and detailed clinical and laboratory studies. Every effort was made to ascertain the presence of potentially disturbing complications, and the possible influence of the several individual conditions elicited will be discussed later in the text.

The surgical cases either present one or more previous subtotal thyroidectomies or an earlier bilateral ovariectomy; a few exhibited both. Those of purely functional origin are limited to pituitary-thyroid and pituitary-pancreas combinations. The latter has been reported from time to time in the more authoritative endocrine literature; the former as a possibility is apparently gathering form and substance as an entity as our knowledge of pituitary agencies is being enlarged and formalized. In 2, at least, of our 5 non-surgical thyroid-pituitary cases the association was certainly no more than a sequential one. Earlier pituitary malfunction had produced characteristic stigmata,⁵ which persisted into the later adult years at the time when the individual was being studied. At this time of examination the thyroid influence determined the diagnostic pattern. With the diversity of influences, operating quantitatively and directionally, which this small group presents, it is a matter of no little difficulty to collate even the limited data of the carbohydrate metabolism within reasonable compass. Substituting the symbols +, = and — for respectively hyperfunction, dysfunction and hypofunction, certain of the pertinent material may be collated.

The prevailing ages are high in comparison with the cross-section of the average diagnostic service which contains these several endocrine entities. As the low ages indicate, an occasional

younger person falls in one or another category, but such occurrence is rare. Seemingly the time factor for the development of the presenting conditions is a considerable one, a situation which could well have been anticipated.

TABLE 3.—AGE.

	Group.		High.	Low.	Average.
1-a	P ±, T ±		63	36	47
b	P —, T —		56	51	54
2-a	P —, G —		56	18	47
b	P ±, G —		50	30	42
3-a	T +, G —		60	41	52
b	T ±, G —		56	26	43
c	T —, G —		54	19	40
4-a	Pan —, P ±		56	26	39
b	Pan —, G —		63	57	60

The blood and urine data reflect certain aspects of the sugar metabolism.

TABLE 4.—BLOOD AND URINE DATA.

Group.		Glycosuria.		Blood sugar.		
		% +.	Amt. (av.).	High.	Low.	Av.
1-a	P ±, T ±	33	Traces	104	84	98
b	P —, T —	0	..	107	96	102
2-a	P —, G —	0	..	118*	83	96
b	P ±, G —	60	Traces	108	90	96
3-a	T +, G —	67	Trace	85	98	90
b	T ±, G —	0	..	111	89	101
c	T —, G —	0	..	100	68	86
4-a	Pan —, P ±	75	12 gm.	290	145†	212
b	Pan —, G —	100	44 gm.	230	223	227

* Emotional response.

† Insulin.

In the main, the prevailing blood-sugar levels fall within the conventional normal range and present nothing distinctive; the same is true for the uncomplicated individual endocrinopathies. A predictable exception to the above is found in the hyperglycemia of the diabetics, while the castrates with thyroid failure show a low normal level.

The agencies strongly depressing tolerance are pituitary dysfunction, thyroid hyperfunction and ovarian and pancreatic failure. The incidence and amount of glycosuria reflects these influences in the several subgroups, exception being where the powerfully augmenting influence of pituitary failure is manifest, and less strikingly in Group 3-c, where thyroid failure opposes the depressing effect of castration. Only among the diabetics does the sugar elimination reach significant proportions, 1 or 2 gm. or even less being the usual report from the other positive urines.

In reporting the observed galactose tolerance it should be borne in mind that the actual number of cases in any one subgroup is very small, and also that within the series wide variations occur in the degree of the incretory involvement. This, of course, is not the

case with the castrates, all of whom present a complete hypogonadism, but it applies specifically to all of the complementary functional derangements and even to those presenting the end results of subtotal thyroidectomy. For this reason, high and low values are recorded as indicating the scatter within the single class. The averages are to be regarded only so nearly representative as the small number of cases warrants. In 3 of the subgroups the tolerances were identical, but the groups were small and additional cases, in all probability, would have recorded differences.

TABLE 5.—GALACTOSE TOLERANCE.

Group.			Deviation (%).		Average.
			High.	Low.	
1-a	P ±,	T ±	-85	-25	-57
b	P -,	T -	+71		+71
2-a	P -,	G -	+100	±0	+20
b	P ±,	G -	-75		-75
3-a	T +,	G -	-75		-75
b	T ±,	G -	-75	-25	-61
c	T -,	G -	-50	-25	-40
4-a	Pan -,	P ±	-50	-43	-48
b	Pan -,	G -	-75	-50	-63

In Group 1-a both factors tend to depress tolerance, while in 2-a both exercise an opposite effect, that of the pituitary being the most powerful augmenting influence of which we have record.

In Group 2-a the depressing effect of castration is outweighed by the pituitary influence and a moderate increase results. With the dysfunctional pituitary, the effect is to lower tolerance, and this reinforces the like influence exercised by castration. In the three thyroid-ovary groups the average values show roughly the progress from significant reinforcement to a terminal partial compensation of ovarian depression as the hormonal activity of the first gland declines.

In the fourth group, in which the pancreas is one of the component factors, the pituitary (a) seemingly exercises but slight influence, the average being that earlier recorded for uncomplicated diabetes (Table 1). On the other hand, castration exercises its invariable depressing effect and that in women of fairly advanced age, certainly beyond the natural menopausal boundary.

While recognizing that any arithmetical expression with such small numbers of cases and with the variations in degree of functional involvement within the group can define no more than a trend, the consistency of the postulate may be roughly estimated by such an approach. Taking the deviation values from Table 1 for the uncomplicated influence of each entity, their algebraic summations give a calculated value for each of our present subgroups. A single exception is made in the use of -50% for the surgical hypogonad case, the figure in Table 1 including mild functional

derangements and thus lessening the average deviation from that of total failure.

TABLE 6.—CORRELATIONS.

Group.		Number of cases.	Tolerance deviation (%).	
			Calculated.	Observed.
1-a	P ±, T ±	6	-71	-57
b	P -, T -	2	+76	+71
2-a	P -, G -	11	+21	+20
b	P ±, G -	5	-99	-75
3-a	T +, G -	3	-108	-75
b	T ±, G -	7	-72	-61
c	T -, G -	7	-45	-40
4-a	Pan -, P ±	4	-97	-48
b	Pan -, G -	2	-98	-63

Before discussing the degrees of correlation, one point must be considered. There is a definite and intrinsic arithmetical limit to the numerical expression of depression; in addition, with but one exception (-85% in Group 2-a), none of the subjects in the present series were tested with less than 10 gm. of sugar, thus defining a maximum deviation of -75% .

On this basis, Groups 1-b, 2-a and 3-c show a high, and 1-a and 3-b a satisfactory, degree of correlation. In Groups 2-b, 4-b and, most significantly, 3-a, the summation of the influences exhibit the limitation of the arithmetical approach with calculated values that exceed those which could possibly be reached under the convention of the testing. Even in these groups the reinforcing influence of one depressing agent upon its fellow is clearly manifest. In short, with the single exception of Group 4-a, in which the pancreas and pituitary participate, there is complete harmony in direction and a rough, consistent approximation in degree. In fact, the closeness of correlation in Groups 1-b, 2-a and 3-c must be regarded as fortuitous.

Turning for a moment to the one divergent comparison and recognizing that the predicted value of -97% is equivalent to no more than a -75% for the observed, we find that the 4 cases comprising the series showed, respectively, -25% , -43% , -50% and -75% . Conventionally these were all designated as dysfunctional states of the pituitary, but if only one (that at -25%) were adjudged to be a pituitary failure, the calculated deviation would become -70% , or in most satisfactory concordance with the observed average. While this offers a plausible explanation of the discrepancy in this group, the far-reaching effect of so minor a manipulation again emphasizes the need of considering the numbers as recorded as no more than rough indices of relative magnitudes.

In the earlier paragraphs mention was made of disturbing effects from non-endocrine agencies. The few cases in the series where such conditions obtain may be briefly reviewed.

There were 4 cases with actual or potential neural injury, including

1 postencephalitic, 2 cases with previously fractured skulls, none of whom gave positive evidences of current neural abnormality, and 1 with intrasellar tumor. This last case was a woman, aged 39, a diabetic, and was the patient showing the minimum deviation of -25% in the galactose tolerance. While, as previously noted, she was recorded as of dysfunctional pituitary status, the galactose level, aside from other considerations, would seemingly indicate a partial compensation, through pituitary failure, of the depressing pancreatic influence. A modest further support is found in the blood-sugar level of 163 mg., the lowest recorded in the non-insulinized diabetic group. Finally, her urine was free from sugar, the only case in the group. In view of the experimental results previously noted,² this case assumes peculiar interest. Two of the other neural cases gave tolerances consistent with their respective endocrine status; the third is discussed below.

Four cases gave evidence of some degree of hepatic dysfunction, of which 3 showed tolerances seemingly defined by the endocrine status. The remaining case may receive brief comment. The patient was a woman, aged 48, with an earlier history of encephalitis but without demonstrable residua. There was definite hepatic dysfunction; the endocrine status was a pituitary failure with surgical hypogonadism. She responded first to a test meal of 80 gm. or +100%. Her predicted tolerance would be increased, but only to a moderate degree, as the ovarian depression operates against the pituitary. The observed tolerance—uniquely high for this group—may be ascribed to the hepatic influence. While ordinarily liver disorders depress sugar tolerance, we have recorded⁶ a small number of cases in which the opposite condition obtains. True, one could assume a dominant pituitary effect here, and, indeed, such may be the case. The other explanation is a possibility that warrants mention.

To complete the tale of non-endocrine factors, there were 2 psychotic and 1 psychoneurotic patient in the series, all of whom gave no evidence of a superimposed effect from this cause. The limits of variation in most of the subgroups were sufficiently elastic to absorb moderate additional effects without changing the sign of the observed deviation.

Summary. This material appears to support the postulate, that the end result of the galactose tolerance, as observed in the individual human being, reflects the algebraic summation of the several influences where more than one is operative. This emphasizes alike the need for caution in the interpretation of a single evidence and the unwisdom of establishing a diagnosis on an unsupported single end result, common to a number of causes, in terms of one of them. Seemingly, the utilization capacity for galactose in the human being is influenced by a number of agencies not demonstrably inter-related with each other and capable of independent functioning.

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BOOK REVIEWS AND NOTICES

NUTRITION AND DISEASE. The Interaction of Clinical and Experimental Work. By EDWARD MELLANBY, M.D., F.R.C.P., F.R.S., Late Professor of Pharmacology, University of Sheffield; Consulting Physician, Royal Infirmary, Sheffield; Secretary of Medical Research Council. Pp. 171; illustrated. London: Oliver & Boyd, 1934. Price, 8/6.

THIS short volume of 170 pages, packed with interesting experimental data and clinical observations, is a fine illustration of the interaction of Laboratory and Clinic.

The material presented represents the essence of the Croonian Lectures delivered before the Royal College of Physicians in June, 1933, and includes chapters on Rickets, Dental Structure and Disease, and a noteworthy discussion of disorders of the Thyroid Gland. The section on Nutrition and Infection, discussing particularly puerperal sepsis and septicemia, presents information of practical importance to obstetricians and surgeons.

Of especial interest is the discussion of Nutritional Influences on the Nervous System, in which the author correlates experimental work on animals with pathologic changes observed in pernicious anemia, subacute combined degeneration, disseminated sclerosis and xerophthalmia. It is stated that whereas watery extracts of liver may improve the blood picture of pernicious anemia, the protective agent against cord degeneration is a fat soluble factor, namely, vitamin A. Commercial liver extracts do not prevent nervous degeneration in dogs on a diet deficient in vitamin A. Thus Mellanby believes that whole liver plus vitamin A, used over an extended period of time, is the best therapy for pernicious anemia.

The work is generously illustrated with charts, sketches, clinical picture and microphotographs. The illustrations of nervous system lesions of nutritional deficiency origin are particularly noteworthy. The author has a pleasing style with plausible arguments and logical deduction.

This small book is a substantial contribution to the study of Nutrition and Disease.

E. B.

KREBS IM LICHTE BIOLOGISCHER UND VERGLEICHEND ANATOMISCHER FORSCHUNG. By MED. DR. JOSEF LARTSCHNEIDER, LINZ A. D. DONAU. II. Band, Heft 2, Adenomkrebs Kystom Scirrhus Bindegewebe Mesenchym Sarcom Odontom Kieferkystom. Vienna: Franz Deuticke, 1935. Price, M. 7.

IN the second volume the author continues to propound his dubious conceptions of the histogenesis and biologic behavior of malignant tumors. There are, moreover, several chapters dealing with subjects having no relation to the cancer problem, such as a polemic discussion of the character of Virchow and its relation to cellular pathology, explanations concerning the causative mechanism of death in empyema, etc. A few quotations of the dogmatic assertions may best illustrate the type and scientific value of the book.

Basing his discussion of the histogenesis of adenocarcinoma mainly on the findings made by Eberth, in 1868, on multiple cystadenomas of the skin in one frog, the author asserts that they are of carcinomatous character and did not kill the frog because adenocarcinomas are of muscular

origin and represent a collagenous, glue-producing cancer tissue which is unable to attack the parakeratotic covering of the frog. These "adenocarcinomas" in the frog's skin are according to Dr. Lartschneider irritatively formed coelom cavities and vestigial nephridium formations. As undifferentiated mesenchymatous cells are first transformed into spindle-shaped muscle cells, then into myoepithelial cells, and finally into columnar epithelial cells, and, as the replacement of desquamated epithelial cells of mucous membranes is accomplished by a proliferation of the cells of the muscularis mucosa and muscularis, the gigantic hypertrophy of the muscular tissue in the stomach, intestine and bladder in the presence of desquamative processes of the epithelial lining of these organs finds thereby a ready explanation which nobody should doubt. The marked tendency of mesenchymatous tissue and preskeletal muscle tissue to become transformed into glandular tissue accounts for the occurrence of adenomas and pseudocoelomic sacs in places where normally glandular tissue is not present. Precancerous entodermal proliferations such as found in intestinal polyps may develop either into a cancer of the mucous membrane or may germinate into a mesenchymatous tissue which in turn may change into muscle tissue which after undergoing a chemical and morphologic transformation may turn into a tendineous-aponeurotic connective tissue giving rise to a scirrhus carcinoma. The muscle tissue of the tongue is disposed to adenosis and therefore predisposed to produce adenocarcinomas. The vascular muscle tissue is of cross-striated type. Similar extraordinary statements are made in regard to the cancers of the skin of the hornified type.

The author explains death caused by empyema as follows: Muscle cells germinate in the purulent matter completely independent from the organism. For the production and maintenance of these cells heat is required which is produced and taken from the organism resulting in the causation of fever. In case the empyema is too large the body is unable to supply the necessary heat. The temperature needed for the breeding of cells in the empyema becomes insufficient. The empyema turns into an iceberg which attracts the heat remaining in the body and with the loss of this heat from the organism death results. Any comment to these elucidations appears to be unnecessary.

W. H.

DIET AND PHYSICAL EFFICIENCY. The Influence of Frequency of Meals Upon Physical Efficiency and Industrial Productivity. By HOWARD W. HAGGARD, M.D. and LEON A. GREENBERG, PH.D., of the Department of Applied Physiology in Yale University. Pp. 180; 31 illustrations and 35 tables. New Haven: Yale University Press, 1935. Price, \$3.00.

THE authors studied the influence of the frequency of meals upon physical efficiency and industrial productivity. They state that the quantity and quality of food have received a great deal of attention in recent years, but that the distribution of diet in time has not received the attention it deserves. They utilized the respiratory quotient as an index of muscular efficiency and concluded that the practice common in this country of eating the day's supply of food in three installments does not permit of the greatest efficiency of which the individual is capable. They find that, for the working man and woman as well as for the active growing child, five meals a day yield the maximum efficiency, although these five meals need contain no more calories than the usual three meals. Their conclusions were that on the same amount of food the industrial output of factory operatives may be as much as 10% greater under one mealtime arrangement than under another.

E. W.

SOME THOUGHTS OF A DOCTOR. By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A. With a Preface by SIR W. LANGDON BROWN, M.A., M.D., F.R.C.P., Regius Professor of Physic in the University of Cambridge. Pp. 183. London: H. K. Lewis & Co., Ltd., 1935. Price, 6s.

MANY of the brief essays brought together here appeared in German translation several years ago under the more expressive title, *Gedanken eines Arztes über Seele, Natur und Gott*. Even this cosmic handle fails to define satisfactorily a collection of essays in which are considered eugenics, the psychiatrists, longevity, medical teleology, the blood as a group of organs, suicide and euthanasia, therapeutic fasting and low diet, cell memory, the gambling spirit, war atrocities and myths, among other more and less metaphysical subjects. The essays are replete with the individuality, wit, and intellectual vigor hitherto associated with Dr. Weber's literary work, and it is to be hoped that the vacuous title of the book may neither ensnare the ingenuous, nor mislead the cultured medical man whom it will please most.

W. McD., 2p

FIFTY YEARS A SURGEON. By ROBERT T. MORRIS, M.D. Pp. 347. New York: E. P. Dutton & Co., Inc., 1935. Price, \$3.50.

IN this book a distinguished American surgeon looks back over a fruitful period in the development of surgical technique, and reviews with disarming candor his own and others' contributions, salting the review with spirited reflections along the way. It is a two-fisted tale, not lacking in drama for the layman, which will provide the older medical man with the sometimes dubious pleasures of recollection, and the younger with a stimulating perspective on his craft. Such records as this serve notably both the cause of medical history and the better understanding between layman and physician.

W. McD., 2p.

CHILD PSYCHIATRY. By LEO KANNER, M.D., Associate Professor of Psychiatry, The Johns Hopkins University, Baltimore. With Prefaces by ADOLF MEYER, M.D., LL.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University, and EDWARD A. PARK, M.D., Prof. of Pediatrics, The Johns Hopkins University. Pp. 527. Springfield, Ill.: Charles C Thomas, 1935. Price, \$6.00.

THE author in his introduction makes the following statement: "The present volume, which is offered as the first textbook of child psychiatry in the English language, is offered as an attempt to cover the entire field of children's personality disorders on a broad, objective, unbiased and practical basis."

With excellent prefaces by Dr. Edward A. Park and Dr. Adolf Meyer, the book starts off with a consideration of the various schools of psychiatric thought and follows this with an excellent chapter on the principles of child psychology, giving the reader a good foundation for the chapters which follow on the specific problems to be encountered in the difficult child.

The author's vast experience at the Harriet Lane Home of the Johns Hopkins Hospital and at the Henry Phipps Psychiatric Institute is clearly brought out in his able discussion of every conceivable mental disorder of childhood. He is obviously a great admirer of Dr. Meyer, and the latter's common sense philosophy is everywhere present in the book. The psycho-analytical school is given credit where credit is due, but it is obvious that the author does not consider these methods by and large applicable to the common disorders of childhood.

Principles rather than specific therapeutic procedures are given in the discussion of the treatment of the various disorders. As Dr. Meyer once said, "A child guidance clinic must not be merely a center for the distribution of tricks." Each individual case must be analyzed from every angle. When the physical condition, heredity and environment have all been carefully studied the course of treatment will often suggest itself.

This is a book which should be of interest not only to physicians but to laymen interested in the problem child as well. It is extremely well written, offers a wealth of clinical material, and offers something which has long been greatly needed.

A. McG.

TUMORS OF THE URINARY BLADDER. By EDWIN BEER, M.D., F.A.C.S., Visiting Surgeon, Mount Sinai Hospital; Consulting Surgeon, Bellevue Hospital, New York City. Pp. 166; 52 illustrations; 8 in colors. Baltimore: William Wood & Co., Price, \$3.50.

This brief but comprehensive monograph is of importance because of the author's well known contributions to the therapy of these tumors and his sustained interest in the subject for the past twenty-five years. The book deals principally with the epithelial growths because, the author points out, other types of bladder neoplasms are rarities. The author's concise classification of the epithelial tumors of the bladder forms the basis for his discussion of the symptomatology, pathology and treatment. Typical benign and malignant lesions as they appear through the cystoscope are well illustrated. The cystoscopic pictures of conditions resembling tumors are fully discussed. In the Chapter on the Consideration of Treatment of Bladder Tumors the author points out the fallacy of dogmatism in this field and lists the various procedures which he has found of value. He discusses the indications for these different methods in the management of the various types of neoplasms encountered. The author also discusses other methods used by various groups, although few direct references are made to the extensive bibliography.

J. McC.

NEW BOOKS.

Puerperal Gynecology. By J. L. BUBIS, M.D., F.A.C.S., Consultant in Obstetrics, Gynecologist, Mt. Sinai Hospital, Cleveland; Member of Central Association of Obstetricians and Gynecologists. Foreword by P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College, Philadelphia. Pp. 199; 81 illustrations and 22 tables. Baltimore: William Wood & Co., 1935. Price, \$3.50.

Diseases of the Liver, Gall Bladder, Ducts and Pancreas. Their Diagnosis and Treatment. By SAMUEL WEISS, M.D., F.A.C.P., Clinical Professor of Gastro-enterology, New York Polyclinic Medical School and Hospital; Attending Gastro-enterologist, Jewish Memorial and Beth David Hospitals, New York, etc. Chapter on Surgery by J. PRESCOTT GRANT, M.D., F.A.C.S., M.R.C.S., Professor of Surgery, New York Polyclinic Medical School and Hospital; Attending Surgeon, City Hospital; Director of Surgery, Midtown Hospital. Chapter on Roentgenology by A. JUDSON QUIMBY, M.D., F.A.C.R., Professor of Roentgenology, New York Polyclinic Medical School and Hospital; Visiting Roentgenologist, Broad Street Hospital. Pp. 1099; 358 illustrations, 6 color plates and 21 tables. New York: Paul B. Hoeber, Inc., 1935. Price, \$10.00.

- Tumors of the Urinary Bladder.* By EDWIN BEER, M.D., F.A.C.S., Visiting Surgeon, Mount Sinai Hospital; Consulting Surgeon, Bellevue Hospital, New York City. Pp. 166; 52 illustrations, 8 in colors. Baltimore: William Wood & Co., 1935. Price, \$3.50. (Review, p. 712.)
- La Maladie des Pêcheurs D'Éponges Nus.* By SKEVOS ZERVOS. Pp. 29; illustrated. Paris: Librairie J.-B. Baillière et Fils, n.d. (No price given.)
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- Disorders of the Blood.* Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (NEW ZEALAND), Assistant Pathologist, The Christchurch Hospital, New Zealand; Late Post Graduate New Zealand Scholar, The Middlesex Hospital, and Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital. Pp. 543; 53 illustrations and 12 plates (8 in colors). Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, \$7.00.
- Agents of Disease and Host Resistance.* Including The Principles of Immunology, Bacteriology, Mycology, Protozoölogy, Parasitology and Virus Diseases. By FREDERICK P. GAY, in association with 19 others, all of whom, except 4, are past or present members of the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York City. Pp. 1581; 212 illustrations, 6 colored plates, 125 tables and 61 diagrams. Springfield, Ill.: Charles C Thomas, 1935. Price, \$10.00.
- Anemias y Alimentación.* El Principio Antianémico del Hígado y Los Factores Cualitativos de Los Alimentos (Vitaminas, Aminoácidos, Hierro y Cobre) Tesis Doctoral Premiada Por la Academia Nacional de Medicina in 1935. Prólogo de Gregorio Marañón. By JOSÉ SÁNCHEZ RODRÍGUEZ. Pp. 165; 22 illustrations. Madrid: Ediciones Del Arbol, 1935. (Price not given.)
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- Food and Beverage Analyses.* By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Department of Correction Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island; Assistant Clinical Professor of Medicine and Lecturer in Therapeutics, New York Post-Graduate Medical School, Columbia University, etc. Pp. 246. Philadelphia: Lea & Febiger, 1935. Price, \$3.50.

NEW EDITIONS.

Diseases of the Nervous System. A Text-book of Neurology and Psychiatry. By SMITH ELY JELLIFFE, M.D., Ph.D., Formerly Professor of Psychiatry, Fordham University, and Adjunct Professor of Diseases of the Mind and Nervous System, New York Post-Graduate Medical School and Hospital, and WILLIAM A. WHITE, M.D., Superintendent of St. Elizabeth's Hospital, Washington, D. C.; Professor of Psychiatry, George Washington University, etc. Pp. 1175; 497 illustrations and 13 plates. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, \$9.50.

A Text-book of Fractures and Dislocations. Covering Their Pathology, Diagnosis and Treatment. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Clinical Surgery, Rush Medical College of the University of Chicago; Attending Surgeon, Presbyterian Hospital, etc. Pp. 1000; 1042 illustrations. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, \$11.00.

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas. With a Chapter on Hospital Management of Goiter Patients, by VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 348; 181 illustrations. Third edition, entirely rewritten. St. Louis: The C. V. Mosby Company, 1935. Price, \$7.50.

Human Pathology. A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 433 illustrations, 18 in color. Fourth edition, revised. Philadelphia: J. B. Lippincott Company, 1935. Price, \$10.00.

A Textbook of Laboratory Diagnosis. With Clinical Applications for Practitioners and Students. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, Portland. Pp. 585; 27 illustrations and 10 colored plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, \$6.00.

Clinical Diagnosis by Laboratory Methods. A Working Manual of Clinical Pathology. By JAMES CAMPBELL TODD, Ph.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Section on Clinical Laboratories, The Mayo Clinic. Pp. 792; 370 illustrations, 29 in colors. Eighth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1935. Price, \$6.00.

A Textbook of General Bacteriology. By EDWIN O. JORDAN, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Pp. 825; 202 illustrations. Eleventh edition, entirely reset. Philadelphia: W. B. Saunders Company, 1935. Price, \$6.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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THE USE OF CARBON TETRACHLORID, TETRACHLORETHYLENE, HEXYLRESORCINOL AND RELATED COMPOUNDS IN INTESTINAL PARASITIC INFESTATIONS.

DURING the past decade significant progress has been made in the chemotherapy of intestinal infestations. New compounds have been introduced and some of the older remedies, such as chenopodium and aspidium, have been reinvestigated. In spite of extensive clinical trials, an evaluation of the relative clinical merits of these substances or combinations of these substances is difficult. The purpose of this review is not so much to enter into the controversial topic of the relative merits of anthelmintics as to summarize the pharmacologic and therapeutic properties of these newly introduced substances. The clinical aspect of anthelmintics has been discussed recently by Brown.¹

Carbon Tetrachlorid. In 1921, Hall^{2,3} tested the efficacy of carbon tetrachlorid in dogs, horses and swine, with particular reference to the effect of the drug on hookworms. The use of carbon tetrachlorid as an anthelmintic was suggested to him by the fact that chloroform has been applied alone and in mixtures for the removal of hookworms. In animals carbon tetrachlorid was found by Hall to be only slightly less effective than chenopodium. In view of the fact that carbon tetrachlorid was used about a half century ago as an anodyne and anesthetic, Hall took 3 cc. of the drug in hard capsules. No untoward effect was noted. He therefore suggested its use in man for removal of hookworms and ascarides. He also pointed out that carbon tetrachlorid is a chemically pure drug with definite chemical composition and thus possesses an advantage over chenopodium, which is a mixture of a number of compounds in variable proportions. Following his report this drug was used extensively. The average dose administered for adults is 3 cc., which is usually added to 30 gm. of magnesium

sulphate dissolved in half a glassful of water. The mixture is usually shaken, and swallowed in a postabsorptive state in the morning. No breakfast is eaten until the purge has acted. Following the action of the purge a warm soapsuds enema is given, and the stools are searched for worms.¹ Extensive experience with the drug, however, indicated that toxic reactions occur. Thus Lambert,⁴ reporting his 10 years of experience in the treatment of 286,486 persons with various drugs, has observed 6 deaths from carbon tetrachlorid and 1 death from oil of chenopodium. He gained the impression that patients with a large number of ascarides are more sensitive to toxic reactions. Racial factors apparently also play a rôle, as all severe toxic reactions developed among East Indians. Milder manifestations of the drug were dizziness and sleepiness. "Nurses say that after treatment is given in a native village there is a strange unusual silence for the remainder of the day." Headaches, nausea and vomiting develop frequently. Jaundice and bloody stools may appear. The nature and the treatment of the intoxication have been studied extensively by Lamson, Minot and their associates.^{5,6,7,8} They have demonstrated that the important underlying lesion is central necrosis of the liver. They pointed out that carbon tetrachlorid is extremely toxic, both for chronic alcoholic addicts and for those who drink alcohol immediately after treatment. The relation of alcohol to carbon tetrachlorid poisoning was also demonstrated in animals. Irritation or mechanical obstruction of the intestines by ascarides predisposed to poisoning. Migration and obstruction by the ascarides may follow the administration of carbon tetrachlorid; hence for removal of hookworms it is advisable to administer chenopodium before carbon tetrachlorid is given. Another predisposing factor was undigested food in the intestinal tract. Finally, these authors produced experimental evidence indicating that in the clinical symptomatology calcium deficiency plays an important rôle. In support of this factor they mention that children who are undernourished are particularly susceptible to carbon tetrachlorid. When both the calcium ion and the fibrinogen content of the blood are low, intestinal bleeding may be demonstrable. For the prevention of intoxication they recommend: (a) avoiding the administration of carbon tetrachlorid to patients with ascariasis without preliminary treatment for roundworms; (b) refusing treatment to alcoholic addicts; (c) having the patient avoid alcohol and food shortly before and after carbon tetrachlorid administration; and (d) insuring an adequate calcium reserve in all persons treated.

Because of these unpleasant and toxic reactions, attempts have been made to find a more suitable preparation. The early work in this field was carried out in the Zoölogical Division of the United States Bureau of Animal Industry.

Tetrachlorethylene. Hall and his associates have found that among the substances related to carbon tetrachlorid, such as ethylene dichlorid (C_2Cl_2), carbon trichlorid (C_2Cl_3) and tetrachlorethylene (C_2Cl_4), only the latter held therapeutic promise. They found that in experimental animals tetrachlorethylene was as effective as carbon tetrachlorid for hookworms and ascarides. In the first publication Hall and Schillinger⁹ believed that the safety of and lesions induced by tetrachlorethylene are about the same as those observed following the use of carbon tetra-

chlorid. Lamson, Robbins and Ward¹⁰ undertook the investigation of tetrachlorethylene and they observed that this substance is less toxic than carbon tetrachlorid and that it produces entirely different reactions. Tetrachlorethylene is absorbed little if at all from the intestinal tract of dogs in the absence of fat. With massive doses, particularly if fat is present in the bowels, absorption may take place, resulting in intoxication and even death. The manifestations of intoxication, however, are those of a hypnotic and not those secondary to liver damage. Experiments actually failed to reveal necrosis of the liver or lesions of the kidneys. These authors suggested that "the chances of its being toxic in human beings are very slight," and they concluded that from a pharmacologic point of view tetrachlorethylene is superior to carbon tetrachlorid and chloroform for anthelmintic uses. No extreme dietary preparations are necessary. Lamson also predicted that it could be used in the treatment of hookworm disease with far greater safety than either oil of chenopodium or carbon tetrachlorid. Experienced gained by workers in the field confirmed this contention. In certain patients dizziness and giddiness may occur following the usual adult dose of 3 to 4 cc.¹¹ In his extensive experience Lambert⁴ observed no fatalities or severe intoxication. He states, however, that the exhilarating effect is more pronounced than that of carbon tetrachlorid, though some of the bizarre manifestations among natives of the tropics are due to post-treatment hysteria rather than to the drug. It is advisable to refrain from taking fat or alcohol during the treatment. It has been estimated that as high as 77 to 97% of the hookworms were removed after a single treatment with tetrachlorethylene.¹²

Hexylresorcinol and Related Compounds. These substances have been introduced in an attempt to find a safe and effective ascaricide, in view of the fact that both santonin and oil of chenopodium may cause severe intoxication if not properly eliminated. The effective elimination of ascarides is an important problem, not only *per se*, but also in connection with hookworm campaigns. It has been found that both carbon tetrachlorid and tetrachlorethylene cause migration of the ascaris, which may result at times in fatal obstruction of the gut and air passages. The ascaris should therefore be removed before applying these drugs for hookworm eradication.

Lamson, Brown, Robbins and Ward¹³ have found that hexylresorcinol fulfills the requirements for the safe eradication of ascaris infestation. It is active on ascarides *in vitro*, killing them without initial stimulation, and is relatively non-toxic. They have treated 1500 human cases with crystallin hexylresorcinol without any symptoms of consequence and with no instance of ascaris migration, and they have succeeded in removing a high percentage of both ascarides and hookworms, as well as numbers of trichuris. The drug was administered in hard gelatin capsules. Doses of 1 gm. were given to patients of 12 years or over, 0.6 to 0.8 gm. to those from 6 to 12 years, and doses of 0.4 gm. to very young children. In adults, doses below 0.5 gm. were less effective. The efficacy of hexylresorcinol was found to be greatly reduced if food was taken shortly before or after treatment. It was therefore found best to institute treatment in the morning before breakfast, allowing no food for 4 or 5 hours afterward. Full therapeutic doses removed between 90 and 100% of ascaris and hookworms in controlled

cases, so that administration of larger doses seemed unnecessary. In the group of field treatments reported by these authors an average reduction of 90% of ascarides, 80% of hookworms and 55% of trichuris was obtained. A few patients complained of slight gastric irritation and an occasional patient vomited. This was probably due to the irritant action of hexylresorcinol on the gastric mucosa, caused by the interaction of this substance in concentrated form with the protein of the superficial epithelium. On account of the insolubility of hexylresorcinol, this reaction of the mucous membrane is entirely superficial.

Brown¹ claims that tetrachlorethylene is more effective than hexylresorcinol in the removal of hookworms, and therefore is to be preferred for mass treatment. In children and in debilitated and pregnant persons hexylresorcinol is useful. Molloy¹⁴ has used hexylresorcinol in 1784 treatments of hookworm and other intestinal helminth infestations. With the exception of slight gastric irritation, no toxic symptoms were observed. On account of the action of hexylresorcinol on gelatin, he administered the drug in sugar-coated pills rather than in gelatin capsules. Full therapeutic doses of 1 gm. removed from 65 to 72% of hookworms under field conditions. He claimed that in the treatment of ascaris infections the drug is probably without an equal. From 93 to 98% of the ascarides harbored by the individuals treated were expelled by a single dose. In the treatment of whipworm infestations, on the other hand, the drug appears to be less effective than was indicated by other workers. Even so, it was found to be the most effective drug available against this parasite. The administration of a purge 2 hours after the drug lessens its anthelmintic effect. On account of its delayed action, phenolphthalein may be administered simultaneously with hexylresorcinol without lessening its efficiency against hookworms and ascarides. If saline purgatives are employed, they should preferably not be administered until the following morning. In the treatment of hookworm disease a single dose of hexylresorcinol lessens the worm burden to the extent that the patient is relieved of most of his symptoms. It does not, however, entirely eliminate the danger to others, since the majority of individuals treated still harbor a sufficiently large number of worms to be considered "carriers."

Recently Lamson and his associates reported further anthelmintic studies on alkyl-hydroxybenzenes.^{15,16,17,18} A number of alkyl-polyhydroxybenzenes have been studied for their anthelmintic action *in vitro*. Marked ascaricidal properties appeared first in the amyresorcinol and reached a maximum in hexylresorcinol. With the majority of alkylphenols the active substance will be found to occur in a solution range of from 1 to 1000 to 1 to 35,000. The melting point of the active substances is usually below 80° C.; compounds with higher melting points cannot properly come in contact with the worm and are usually ineffective.

The pharmacologic properties of hexylresorcinol have also been reinvestigated and compared with those of other substances. Its absorption and excretion have been studied quantitatively. It is of interest that no consistent lesion has been found except the local irritant effect on the gastro-intestinal tract. Hexylresorcinol was found again to be an extremely effective ascaricide, doses of 0.1 gm. per year of age up to adult doses of 1 gm. removing between 90 and 100% of

the parasites. It is less effective against hookworms, although between 70 and 80% of these parasites can be removed by a single dose. Except for its local irritant properties which cause some temporary, superficial irritation of the stomach and intestine, an effect which is unnoticed by the majority of individuals, hexylresorcinol may be considered from the experiments presented as a non-toxic substance. No case of intoxication has been reported, even after its use in many thousands of individuals.

From the studies of many polyhydroxybenzenes, Lamson and his associates feel that a certain degree of local irritant action must be present in order to allow anthelmintic activity. Anthelmintic activity is not, however, directly proportional to local irritant action. Thus the lower members of these 4-n-alkyl-resorcinols are even more irritating than hexylresorcinol, but they are not such active anthelmintics.

In spite of the fact that it was thought by these workers that the ascaricidal properties were related to the presence of the hydroxyl groups of the benzenes, the dihydroxybenzenes were not found strikingly different in their ascaricidal action from the monohydroxybenzenes. The ascaricidal properties of phenols and resorcinols are increased by the introduction of alkyl radicals. These properties become more marked as the alkyl chain is lengthened, reaching a maximum which differs in different series, and falls off rapidly in the higher members. No significant difference was found between ortho- and para-alkylphenols. The effect of other types of alterations in the structure of alkyl-hydroxybenzenes on the pharmacologic properties of the drug is discussed.

Among the substances studied there are several which theoretically should be as good human ascaricides as hexylresorcinol. There is also a possibility that some of these substances will be found of especial value in other helminth infestations, such as uncinariasis or trichuriasis. Lamson suggests that the efficacy of these substances should be tested in man.

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RADIOLOGY

UNDER THE CHARGE OF
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Mediastinal Tumors. The management of intrathoracic disease is peculiarly the responsibility of the roentgenologist, in the opinion of Evans and Witwer,² for his is the method of accurate detection, differential diagnosis, indication and guide in therapy, and in certain cases his may be the healing agent necessary for the optimum result. This applies particularly to intrathoracic and more especially to mediastinal neoplasms, conditions which were rarely recognized in the pre-Roentgen period and, if recognized, could not be successfully treated by methods known at that time.

Mediastinal neoplasms of all types represented less than 1% of all the neoplasms coming under their observation over a 12-year period.

Primary tumors may originate in the lymph nodes, connective tissues, thymus or thyroid gland, and in the bloodvessels of the mediastinum. In the benign group they observed: (1) Cysts (echinococcus, dermoid, etc.); (2) ganglionic neuroma; (3) fibroma; (4) chondroma; (5) lipoma; (6) aneurysm. Pathologists vary in opinion as to the histogenic nature of many of the malignant neoplasms, but, for practical purposes, they have found a satisfactory grouping to be: (1) Lymphoma (lymphosarcoma, pseudoleukemia, aleukemic leukemia, malignant granuloma,

Hodgkin's disease and thymoma); (2) sarcoma, as a rule originating from areolar connective tissue (fibrosarcoma, spindle-cell sarcoma and alveolar cell sarcoma); (3) carcinoma of thymic and thyroid origin; (4) teratoma. The essential clinical features are well known, but they particularly mention some unusual clinical features as they enter into the technique of Roentgen therapy. Very large tumors, in addition to the symptoms of respiratory embarrassment, may produce marked edema of the neck and face. Since heavy radiation treatment may increase edema and respiratory difficulty, it sometimes appears advisable to resort to the fractional method of treatment with smaller doses in cases in which the indications for such a procedure exist. Hemorrhage is a relatively rare but important complication in tumors primary in the mediastinum.

Roentgen examination should include fluoroscopic and roentgenographic examination, in the latter a study in the lateral position is most important. In addition to the information regarding the size, shape, configuration and location of tumors, secondary changes may be demonstrated which are the effect of pressure changes on surrounding structures. Outstanding among these are atelectasis of all or part of one or more lobes, and pleural effusion, the latter is not necessarily an indication of pleural metastases, it can be the result of pressure.

In their experience, shadow changes produced by some of the mediastinal tumors are not always constant and expansile pulsation is not always a safe index of an aneurysm in differential diagnosis. Visualization of the esophagus with the aid of barium, to detect encroachment upon its lumen, the intratracheal installation of lipiodol and the induction of pneumothorax to better define the tumor are aids in diagnosis. For the past 10 years an increasing effort has been made to utilize the variation in the radiosensitivity of mediastinal tumors as a guide in their differential classification. The largest dose over the tumor which can be tolerated without injury to the normal tissue (as a rule, 110 to 130% skin unit dose) is given, the variation in response of tumors is then estimated and used as an index. From the response to radiation, certain conclusions may be formed concerning the morphologic nature of the tumors irradiated. Tumors arising from the lymphocytic cell element, such as lymphosarcomas, thymomas, pseudoleukemias and lymphatic leukemias, will entirely disappear within from 4 to 10 days following the administration of a therapeutic test dose. Tumors originating from the reticulo-endothelial cells of the mediastinal lymph glands and the thymus, such as Hodgkin's disease, Sternberg type of hyperplastic tuberculosis, and endothelioma, respond more slowly, being reduced within 10 days following the administration of a therapeutic test dose to one-half their original size, and disappear entirely in about 6 weeks or longer following the treatment. Primary mediastinal tumors having their origin from the areolar tissue (such as fibrosarcoma, large round cell sarcoma, carcinoma of the thymus and thyroid glands and teratomas) show some reduction in size following exposure, but rarely disappear at the end of 6 weeks. Benign tumors of the mediastinum (lipoma, chondroma, fibroma, neuroma, dermoid) or pseudo tumors (aneurysm, mediastinal abscess, mediastinal effusion) with the exception of fibroma, which responds very slowly, are not influenced by radiation.

Extrapulmonary Tumors of the Thorax. Pierce⁴ divides these into: (1) Tumors of the thoracic wall proper, which include lipoma, fibroma, myxoma, chondroma, osteochondroma and angioma in the benign group and chondrosarcoma, osteochondrosarcoma, osteogenic sarcoma of the ribs, "giant sarcoma," myxo-angio-endothelioma in the malignant group. Metastatic malignant neoplasms may involve the thoracic wall. Ganglioneuroma and neurofibroma (neurinoma) occur rarely in the thorax, the former will appear predominantly in the posterior or paravertebral gutter or the mediastinum, the latter most commonly is associated with the intercostal nerves. The neoplasm tends to be either sessile or nodular in the thoracic parietes or globular when found in the posterior gutter or mediastinum.

Tumors of the pleura of extrinsic origin include chiefly metastatic malignancy, echinococcus cyst, tuberculoma and fibrinoma, those of intrinsic origin, endotheliomas and the connective tissue tumors such as chondromas of the phrenic pleura, are rare. Lesions which properly do not arise from the thoracic wall or pleura, but which may present Roentgen changes by pressure or invasion in the wall or pleura are chiefly aneurysms of the innominate artery, new growths from embryonal rests (teratoma) and the so-called "superior pulmonary sulcus tumor" (which is probably a primary carcinoma from the pulmonary apex).

Harrington³ surgically treated 47 extrapulmonary intrathoracic growths, of which 26 were benign and 21 malignant. Of these growths 15 were considered to have originated from the spinal root or intercostal nerve sheaths and were grouped under the general term, perineural fibroblastoma. Eleven were classified pathologically as neurofibromas, 2 as cellular fibromas and 2 as fibrosarcomas, which probably were benign tumors originally but had undergone malignant change. Twelve were histologically designated teratomas, 5 of these as dermoid cysts because their structure consisted essentially of ectoderm, in another 4 the tissue elements were derived from all 3 of the germinal layers, and a 5th showed such a high degree of organoid structure that it was designated as a fetal parasite; the remaining 2 of this group were squamous cell epitheliomas, evidently primarily benign tumors that had undergone malignant change.

Two chondromas and 1 osteochondroma completed the series of benign lesions; 1 chondroma was practically within the thorax and was discernible in the anterior portion of the thorax because of the marked calcification of the growth; in the other a moderate sized external mass presented in the anterior wall of the thorax, but the major portion of the tumor was in the thorax and filled practically two-thirds of the thoracic cavity with chondromyxomatous material which was definitely encapsulated. The chondro-osteoma involved one entire rib from the sternum to the spine.

Six cases in the series were classified pathologically as endothelioma; 3 of these originated in the parietal pleura, 1 in the visceral pleura, 1 in the anterior mediastinum and 1 in the posterior mediastinum.

In 11 cases the tumors proved to be sarcoma; in 7 the tumor originated in the bony structures of the wall of the thorax and in 4 it had its origin in the ribs close to its attachment to the vertebra.

The benign tumors summarized were: neurofibroma, 11; cellular

fibroma, 2; dermoid cyst, 5; teratoma, 4; fetal parasite, 1; chondroma, 2; and chondro-osteoma, 1. Of the malignant lesions 2 fibrosarcomas were considered primarily benign perineural fibroblastomas that had undergone malignant change, 2 squamous cell epitheliomas as teratomas that had originated as benign tumors and had undergone malignant change. The remaining malignant tumors were: endothelioma, 6, and sarcoma, 11.

In his experience, roentgenography plays an important rôle in the recognition and differential diagnosis of these growths in many of which surgical treatment offers the greatest hope for complete eradication of the disease. The clinical manifestations of these tumors are often meager and rarely pathognomonic, although they are always of value when correlated with the roentgenologic findings in establishing a final diagnosis. A study of early cases has proved that a relatively high percentage of the lesions is benign, but he believes that these tumors are potentially malignant.

The roentgenologic technique suggested is similar to that already mentioned; also the use of radiation therapy as an aid in differential diagnosis.

As evidence that the perineural fibroblastomas (commonly neurofibroma) are the most silent tumors within the thorax when they are benign, he states that 4 of the 15 were incidental roentgenographic findings during the course of a general examination. When these tumors do produce symptoms they are usually pressure symptoms due to mechanical interference as a result of location and increasing size. If these tumors undergo malignant change, pain becomes a feature, rather marked and more severe at night. These growths were the most common in the posterior mediastinum in his series, 13 of the 15 were located here, one was a dumb-bell or hour-glass tumor situated in the posterior mediastinum and the spinal canal and one was situated in the lateral wall of the thorax.

Roentgenographically they usually present a circumscribed shadow, rounded in contour, with a sharp border, situated usually in the posterior mediastinum. Sometimes the tumor is lobulated, but the borders are practically always sharply outlined. In those cases in which the tumor arises within the intervertebral foramen or spinal canal, the pedicles and laminae of the vertebrae on the affected side are eroded and may be completely destroyed. There is enlargement of the intervertebral foramen, and as the tumor enlarges in the posterior mediastinum, sufficient pressure may be exerted to produce widening of the intercostal spaces and pressure erosion of adjacent ribs.

The lesion most commonly to be considered in the differential diagnosis of this group of tumors is aneurysm of the arch or descending portion of the aorta; roentgenoscopic examination of the thorax will usually determine whether the shadow is expansile or non-expansile. Sarcoma originating from the vertebrae or ribs can usually be differentiated because of the more extreme pain and the infiltrating destructive type of erosion of the involved ribs and vertebrae. Endotheliomas originating in the posterior mediastinum in early cases may be difficult to differentiate from neurofibromas, as endotheliomas are practically symptomless, in later cases their roentgenographic image is irregular in outline and the pleural effusion may be bloody. Pleural effusion

may be associated with any of these tumors, although it is not common. A tumor may be the cause of a pleural effusion and a benign tumor may be associated with a bloody effusion.

The teratoma group are the most common type of tumors in the anterior mediastinum; 11 of the 12 tumors in his series originated here. In 5 cases the tumor extended into the left thoracic cavity, in 4 into the right, and in 1 into both the right and the left thoracic cavities. The fetal parasite was confined to the anterior and superior mediastinum and presented just above the suprasternal notch. In the remaining case the tumor apparently originated in the right side of the diaphragm, and it may have originated from cell occlusion with improper fusion of the septum transversum and pleuroperitoneal membrane at the time of closure of the diaphragm. The usual clinical course in these cases is essentially that of an inflammatory lesion, consisting of pain in the mediastinum and dyspnea, and with a sense of pressure, often associated with a sore throat, which is commonly diagnosed clinically as pleurisy and pneumonia.

The roentgenologic manifestations of these growths are not as clear cut as those of other types of tumor and, even after the most exhaustive roentgenologic study, a definite diagnosis cannot be established. One of the main reasons for this difficulty is the marked inflammatory reaction which is often present, which produces a change simulating an inflammatory or infiltrating type of lesion in the structures surrounding the growth, often obscuring the definite outline of the tumor. The outline of the tumor may be hazy and infiltrating in character when viewed in one plane, but may show a rounded contour when viewed in another. Some may be cystic, and a definite fluid level may be visualized with its surrounding sac. On roentgenoscopic examination most of the growths present a transmitted pulsation due to their attachment to the pericardium at the base of the great vessels and great care must be exercised in differentiating these lesions from aneurysms of the arch or descending aorta.

Radiotherapy as a therapeutic test is often of aid in establishing a diagnosis by ruling out the presence of lymphoblastoma, which is one of the most common tumors to be considered in the differential diagnosis. Other conditions to be considered in the differential diagnosis are thymoma, substernal goiter and mediastinal abscess. There is no distinctive roentgenologic manifestation of endotheliomas, because of the great variation in size and character roentgenography has its greatest value in determining the extent and exact situation of the growth and in ruling out the complications that might contraindicate surgical intervention.

The outstanding symptom associated with sarcoma is pain, first intermittent in character and later becoming more or less constant; it is often more noticeable at night, and usually severe in type. The roentgenographic image shows dissolution of the bone contour, destruction of bone and secondary involvement of the surrounding soft tissues. In cases where neurofibroma has undergone malignant change, it may be impossible to make a definite diagnosis on roentgenologic findings or clinical symptoms.

Although roentgenologic studies of the thorax may be said to give the most important evidence in the clinical diagnosis of intrathoracic

tumors, they are of even greater importance in those cases which are considered for surgical treatment, not only for their assistance in the selection of operable growths, but also because of their aid in determining the most accessible type of approach to the tumor as well as the presence of conditions that might after operation become complications.

In a study of aneurysms of the innominate artery it was quite apparent that the diagnosis of aortitis must first be made. Warfield⁶ found they do not occur without involvement of the aorta. The innominate aneurysm can be described as a superior mediastinal tumor arising on the right side at the upper level of the arch of the aorta and extending above the inner end of the clavicle. In extremely large aneurysms the shadow will extend over the left side. Compression of the trachea is a constant finding, displacement of the trachea to the left is not common. This compression, together with constant beating against the trachea, frequently produces decubitus ulcers. Expansile pulsations were elicited in only 1 of 20 cases, organized thrombus was found in the aneurysmal sac in 12 cases that were autopsied. Transmitted pulsation was seen in nearly every case. In differential diagnosis, a saccular aneurysm arising from the upper portion of the right aortic arch lacks the characteristic semicircular contour of an aneurysm of the innominate artery. It does not produce compression of the trachea nor does it present a palpable transmitted pulsating mass in the supraclavicular space. A unilateral substernal thyroid on the right side depresses the arch of the aorta downward and displaces the trachea to the left, widens from below upward, moves with the trachea and shows no transmitted pulsation. Dermoid cyst and tuberculosis rarely cast similar shadows.

Cysts of the Lung. Dubrow¹ reviewed the literature on congenital cysts of the lung and grouped these lesions under two divisions: (1) symptomatic and (2) asymptomatic. The latter embraces those solitary or multiple cysts with an open bronchial connection which is frequently discovered during roentgenographic examination for some other condition. The theories of their etiology explain to an extent the roentgenologic findings. Defective embryologic development of the bronchi results in complete or incomplete stenosis of the main bronchus or bronchi, usually of the upper lobe, with distal dilatation of the end bronchus; defective embryologic development of the areolar tissue (alveolar agenesis) which leaves the bronchi unsupported and causes them to be unduly dilated; and defective embryologic development of the lymph vessel systems of the corresponding lung occur. The cysts may be filled with fluid if the deformed bronchus is completely occluded, if incompletely stenosed they will contain air.

The condition may simulate bronchiectasis, pulmonary atelectasis and spontaneous pneumothorax. Lipiodol injection will demonstrate extensive sacculation in contradistinction to acquired massive pulmonary atelectasis in cases in which the main bronchus is completely obstructed. The roentgenogram in cystic lung fails to show any evidence of collapsed lung, the entrapped air being intrapulmonary. Cysts of the lung may be solitary or multiple, or one entire lung may be the seat of cystic degeneration. Schenck and Stein⁵ reported a case of a solitary non-expansile fluid cyst in an infant 5 weeks old with no

symptoms referable to the chest. During a bout of vigorous coughing, the infant raised some thick, tenacious fluid. Roentgenographic examination revealed a horizontal fluid level with air above, which suggested a rupture of the cyst into a neighboring bronchus or bronchiole. Finally the cyst, entirely replaced by air, collapsed and the lesion spontaneously disappeared.

Before the advent of roentgenography the condition was seldom, if ever, recognized during life. Occasionally it is necessary to induce a pneumothorax to establish the diagnosis of congenital cystic lung. Diaphragmatic hernia or eventration can readily be excluded by roentgenoscopic examination after the oral administration of barium.

CHARLES G. SUTHERLAND, M.D.

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ORIGINAL ARTICLES.

URINE FORMATION IN THE AMPHIBIAN KIDNEY.*

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It has been known for some 60 years that the frog's kidney offers opportunities to the physiologic experimenter which are not afforded by the more compact, inaccessible and intricate mammalian kidney. The first practical recognition of these opportunities was made by Nussbaum² who, in 1878, showed that the double blood supply of the frog's kidney might make possible the separate study of the functions of the glomerulus and of the tubule. He ligated the renal arteries, leaving the capillary circulation of the tubules by way of the renal portal vein intact; found that after injection of urea urine was formed and concluded therefore that the epithelium of the tubules contains a secretory mechanism. This famous experiment, refined by Beddard and Bainbridge,³ seemingly unambiguous, has formed one of the firmest supports of the doctrine of secretion by the tubule.

Thirty years later Cullis⁴ utilized the double circulation of the frog's kidney in a somewhat different way by inventing the method of double perfusion. Inserting one cannula into the aorta and another into the renal portal vein or its collateral, the anterior abdominal vein, she showed the possibility of presenting to the tubule of the surviving kidney substances which were not contained in the fluid which was perfused through the glomeruli. This

* A lecture delivered before the Harvey Society by A. N. Richards, January 17, 1935.
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method, subsequently perfected, has been widely adopted particularly in the study of problems of secretion by the renal tubule.

The development of another method for which the frog's kidney, because of its translucency is particularly suited, began in 1920 when, in Leonard Hill's laboratory in London⁵ and in our laboratory in Philadelphia,⁶ this structure was subjected to microscopic study during life. Hill's problem was that of the blood pressure in the glomerular capillaries; ours, the behavior of the glomerular circulation during the action of minute concentrations of adrenalin. Hill confined his study of this preparation to his original problem. In our laboratory a plan developed to attempt the withdrawal by capillary pipettes of fluid from single renal units at different levels of the nephron in the hope that chemical tests or analyses might yield a description of urine at various stages in its elaboration.* Such a plan, if realized, would, it was thought, tell us unequivocally whether glomerular fluid has the composition of a filtrate or whether it is the product of selective secretion; whether processes of reabsorption or secretion or both are operative within the tubule and in what parts of the tubule they occur. Such information in turn might conceivably lead to identification of the means whereby the renal mechanisms are regulated and adjusted to meet the excretory requirements of the body.

In the execution of this plan the first point of attack chosen was the glomerulus, partly because of its size and accessibility; partly also because of the conviction that from the standpoint of orderly experimentation with the kidney it is the most important. So much of our thinking concerning events which take place in the tubule depends for its soundness and fertility upon correct information concerning the volume and character of glomerular excretion that no amount of effort seemed too great if this could be secured.

It was relatively easy to construct a simple apparatus, the essential item of which is a sharply pointed micropipette, with which Bowman's capsule could be punctured and minute amounts of fluid withdrawn. Nor was it excessively difficult to transfer such collected fluids to capillary tubes and to subject them to qualitative tests for various constituents. The results were in general accord with the postulates of the filtration theory of glomerular function, *i. e.*, the glomerular fluid was found not to contain protein, it was alkaline, contained urea, chlorid, reducing substance, potassium, and certain dyes, if these had been injected before the experiment was begun.⁷ These results, first obtained with glomerular urine from the frog, were confirmed a little later by White and Schmitt⁸ with glomerular fluid similarly obtained from *Necturus*.

This demonstrated qualitative resemblance between the glom-

* In the initiation and early development of this plan the collaboration of Dr. J. T. Wearn was most important. Later developments have been greatly assisted by generous financial support from the Commonwealth Fund.

erular fluid and a protein-free plasma filtrate was scarcely adequate to decide the questions which concerned us; quantitative information was necessary; and in getting this, genuine difficulties were encountered because of the minute quantities of fluid available for analysis. To be useful in this connection a quantitative method must be applicable to a volume of fluid of the order of 0.5 cmm. or even less; and in the handling of these quantities of fluid rigid precautions must be adopted against contamination and evaporation. Successful adaptation of existing methods to these requirements has been accomplished which makes possible the following quantitative determinations on from 0.1 to 0.5 cmm. of fluid: total molecular concentration, total electrolytes (electrical conductivity), chlorids, inorganic phosphate, glucose, urea, uric acid, creatinin, pH, and the dyes; phenol red; neutral red and indigo carmine. Each method was tested rigorously by analyses of pure solutions and its accuracy approximately defined.

QUANTITATIVE ANALYSES OF GLOMERULAR URINE AND BLOOD PLASMA

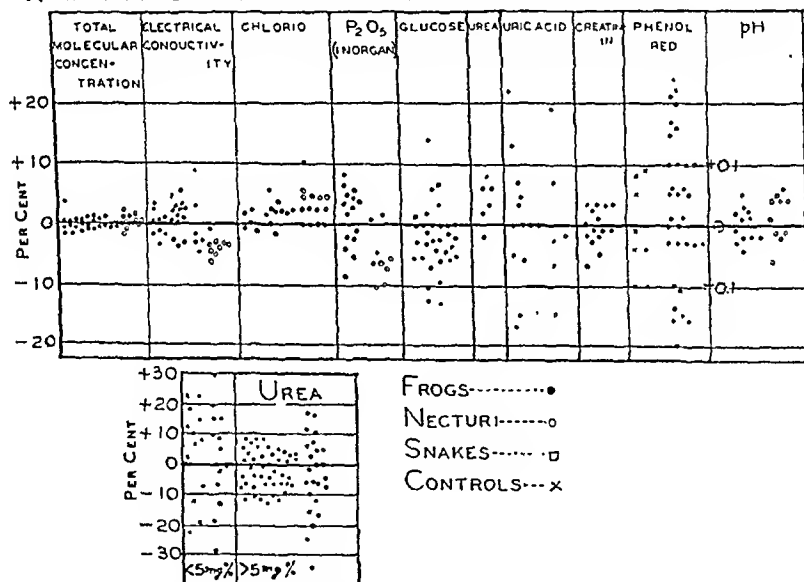


FIG. 1.—The composition of glomerular urine. Results are shown as percentage differences from blood plasma or an ultrafiltrate from it.

Assembled on a single chart (Fig. 1) are the results which have been obtained by applying these methods in quantitative comparisons of the composition of glomerular urine and blood plasma. It includes work with the 2 species, frog and Necturi and a few estimations of uric acid in glomerular urine of snakes. Each circle on the chart represents the result of a quantitative analysis of glomerular urine. Its position above or below the abscissa shows its percentage deviation from the corresponding value in plasma or in an ultrafiltrate from plasma.

The first section shows results of 32 comparisons⁹ of the total concentration of glomerular urine and plasma from the same animal, obtained by Barger's method as adapted by H. L. White¹⁰ for the purpose of this study. Omitted are White's earliest figures which he now regards as erroneous. In almost every case the correspondence represents identity. The results show that in frogs and *Necturi* the total concentration of glomerular urine and of blood plasma are the same, the osmotic pressure being approximately equal to that of a 0.6% solution of NaCl.

The second section shows that the total electrolyte content of the two fluids is the same.¹¹ The third shows that the Cl concentration of glomerular urine is on the average slightly higher than that of plasma.¹² The difference is within the errors of method, but the consistency of its sign indicates that it is not fortuitous. It may be explained by a Donnan equilibrium at the glomerular membrane. Omitted are earlier determinations by Wearn and Richards¹³ and by Freeman, Livingston and Richards¹⁴ by the nephelometric method now regarded as unreliable. Included are five determinations by Ekehorn¹⁵ made by microtitration according to Mohr; the others were made by Westfall and Findley in our laboratory by a recently devised development of Isaacs' colorimetric method, found to be exceedingly sensitive and reliable.

Inorganic phosphates,¹⁶ glucose,¹⁷ uric acid¹⁸ and creatinin¹⁹ were determined by capillary tube adaptations of the methods of Kuttner, Sumner and Folin. The approximately equal distribution above or below the abscissa, the fact that the majority of the figures fall within the average errors of the methods are evidence of identity of concentration of each of these constituents in glomerular urine and plasma.

Concentration of phenol red was determined by simple capillary tube colorimetry.²⁰ Glomerular urine and plasma from a frog previously injected with the dye were made alkaline with NH_3 vapor and intensity of color determined by comparison with standard solutions. Only from 60 to 90% (average, 71) of phenol red in frog's plasma is uncombined with protein and hence filterable. In each case, therefore, 71% of the total phenol red concentration of plasma was taken as the value with which to compare the concentration of phenol red in glomerular urine. The approximately equal distribution of the points above and below the abscissa is regarded as evidence of the probability that had the correction for combined phenol red in plasma been accurately known in each experiment, values of phenol red in glomerular urine and plasma ultrafiltrate would have been more nearly coincident.

pH was determined by Dr. Montgomery²¹ by collecting in quartz capillary tubes glomerular urine from animals previously injected with phenol red, due precautions against loss of CO_2 being taken. Color comparisons were made with standard buffer solutions in

quartz capillary tubes containing approximately the same concentration of phenol red as the glomerular urine.

The urea estimations constitute one of the most important sections of the chart. Only 6 are included, despite the fact that more than 40 other experiments have been made. The reason for this is that the analytical method²² has recently been refined and these 6 experiments are the only ones which have since been made. In a separate section are shown the earlier results. The crosses represent each the result of a microanalysis of a known solution, not known to the analyst. Its position with reference to the abscissa represents the percentage difference between the concentration known and the concentration found. The black circles represent similar microdeterminations of urea in glomerular urine, placed on the chart so as to show percentage difference from urea in the plasma. The first section includes determinations on solutions and samples of glomerular urine in which the concentration was less than 5 mg. N per 100 cc. The second from 5 to 20 mg. per 100 cc. If it is considered that only 1 analysis is required to define the position of a cross, while 2 analyses (1 of glomerular urine and 1 of plasma) are required to give the position of each circle, the greater spread of the circles is understandable. These figures indicate even more convincingly than do the 6 values in the larger chart that the concentration of urea in glomerular urine is the same as that of plasma.

The only conclusion which seems to emerge from this assemblage of data is that glomerular urine has the composition of an ultrafiltrate from plasma; that were the glomerular membrane a structure which could either selectively retard or selectively accelerate the passage of a diffusible constituent of the plasma through it, in some one of the categories represented in this chart a trend of difference between glomerular urine and plasma would be evident. Such a trend is seen in the chlorids, but it is in the direction and its magnitude is of the order which was predicted from our knowledge of the Donnan membrane equilibrium. The conclusion is that this fairly extensive study reveals nothing which indicates that the glomerulus is capable of secreting.

Before citing some further information which confirms and amplifies that already given, it seems necessary to interject two statements, the omission of which would constitute a serious gap in the argument. First concerning blood pressures: If the pressure within the glomerular capillaries is insufficient to overcome the resistance to filtration which the osmotic pressure of the plasma proteins presents, the conclusion that the glomerular process is solely one of filtration would be absurd. The first measurements of glomerular capillary pressure, made by Leonard Hill and McQueen in 1921,⁵ seemed to make it highly questionable that an effective filtration pressure exists in the glomerular capillaries. However, two sub-

sequent examinations of this question have been made, one by Hayman,²³ the other by White²⁴ by a method more direct and believed to be more trustworthy. The results were as follows:

FROGS. (HAYMAN.)		H ₂ O, cm.	Average.
Glomerular capillary pressure		10.0 to 27.0	20.2
Plasma colloid osmotic pressure (Churchill, Nakazawa and Drinker)		1.5 to 13.4	5.3
Filtration pressure		8.5 to 13.6	14.9
NECTURUS. (WHITE.)			
Glomerular capillary pressure		8.5 to 27.0	17.7
Plasma colloid osmotic pressure		6.5 to 14.2	10.4
		2.0 to 12.8	7.3
Intracapsular pressure		0.1 to 2.8	1.5
Effective filtration pressure		1.9 to 10.0	5.8

From these figures we conclude that the blood pressure in the glomerular capillaries is amply sufficient to effect the separation of a protein-free fluid from the blood passing through them.

Second, we must meet the possible criticism that failure to find evidence of a secretory process is due to injury produced by the experimental conditions. The animals (frogs) as a rule are immobilized not by an anesthetic but by destruction of the brain. In opening the abdomen and arranging the kidney for observation, the kidney itself is not touched by instruments and not directly exposed until the puncture is about to be made. The general circulation and the renal circulation is vigorous; when it is not, collection of fluid is impossible. The glomerulus itself is protected by the peritoneum and the capsule of Bowman; its vessels are bathed inside by flowing blood, outside by continually renewed glomerular fluid. Puncture of the capsule can be and usually was accomplished without touching the capillaries of tuft with the tip of the pipette; suction was not used in the great majority of instances in collecting the fluid; reflux from the tubule was prevented by blocking the neck of the tubule by gentle pressure with a microscopic glass rod. We think that despite the necessary mutilation of the animal there is little reason to suspect any consistent direct injury to the glomerular structures.

The further information to which allusion was made a moment ago concerns the glomerular excretion of 4 additional foreign substances after their subcutaneous or intravenous injection. Two of these, indigo carmine and ferric ammonium citrate, are substances the glomerular excretion of which has been denied by those who have studied fixed sections of the kidney excised during their excretion.²⁵ One has only to look at the kidney of a frog during the few moments immediately following the intravenous injection of

indigo carmine to be convinced that it escapes into the capsule of Bowman of every glomerulus through which blood is vigorously flowing. Color comparisons of glomerular urine with known solutions of indigo carmine indicate that its concentration in glomerular urine is approximately the same as that of uncombined indigo carmine in the plasma. These comparisons have not the degree of accuracy of the other determinations listed, hence were not included in the chart.

In each of 10 experiments made by Dr. John Reisinger in which frogs were injected with ferric ammonium citrate, iron was identified in the collected glomerular urine. In 6 experiments in which the kidneys were perfused by way of the aorta with Ringer's solution containing this substance, the concentration of iron in the glomerular fluid was approximately the same as that in the perfusion fluid. The reason why quantitative figures are not given is that we have not yet succeeded in determining the uncombined, filterable iron in plasma. From these facts we believe that the histologic method as it has been applied in the past to the study of the glomerular elimination of these substances has given misleading results.

Neutral red is another substance of interest in this connection. Perfused in Ringer's solution through the frog's renal arteries, it passes into glomerular fluid in the same concentration as in the perfusion fluid. Injected intravenously, scarcely detectable traces can be found in glomerular urine. The reason is that it is almost wholly combined with plasma proteins and hence, except in traces, does not pass through a membrane impermeable to protein.

The fourth substance, inulin, is in a different category from any thus far mentioned. This polysaccharid is non-toxic and can be injected intravenously in large amounts. Its peculiar interest arises from its high molecular weight, and, it is to be assumed, its great molecular-size. Haworth estimated its molecular weight at 5000;²⁶ Irvine at about 3800.²⁷ It is thought to consist of an open chain of 29 or 30 levulose units. It is not hydrolyzed by enzymes of the animal body and after intravenous injection in mammals is quantitatively excreted unchanged in the urine. It was found in a series of preliminary experiments that when injected into frogs or perfused through the arteries of a frog's kidney the glomerular fluid contained it in the same concentration as that in which it existed in the blood or perfusion fluid. The glomerular membrane permits the inulin to pass through it as completely and apparently as readily as urica or creatinin.

By testing the filterability of inulin through artificial membranes we have tried to arrive at a more concrete description of the glomerular membrane. The membranes used were collodion, prepared according to Greenberg and Gunther,²⁸ and DuPont's Cellophane 450 and 600. Through the collodion membrane, inulin, creatinin and NaCl were equally filterable; *i. e.*, the concentration of each in

the filtrate was the same as in the original fluid. Cellophane 450 allowed only 30% of the inulin to pass through; cellophane 600, only 16%; both, however, allowed creatinin and NaCl to pass through in their original concentrations.

If we conceive the passage of fluid and solute through the glomerular membrane to take place through pores in it, we may conclude that these pores resemble in size those of the collodion membrane and are larger than the majority of those in cellophane.

From these results with inulin it may be argued that the glomerular membrane, which permits the filtration of a substance of such large molecular dimensions as may presumably be ascribed to inulin must, *a fortiori*, permit free filtration of the far smaller molecules of the normal urinary constituents. This argument adds support to the conclusion drawn from the analytical data. It is similar to one put forward 4 years ago by Ekehorn,¹⁴ based partially upon the fact that in his experience glomerular fluid collected from frogs usually contained large amounts of protein. In essence he says: If in the glomerular membrane there are holes large enough to permit escape of the huge molecules of protein, that membrane can be nothing else than a sieve for such small molecules as those of urea, etc. Our experience concerning protein in the glomerular fluid differs from that of Ekehorn. The glomerular fluid from normal animals contains no protein or only traces. By traces is meant from 5 to 20 mg. per 100 cc. These minute amounts of protein have been shown by Dr. Qucen in our laboratory to be almost invariably mixtures of albumin and globulin. This seems to mean that here and there in the glomerular membrane, with its myriads of pores, each large enough to permit the passage of inulin molecules, there may be found a few defects large enough to allow whole plasma to pass through; the escape of protein through these does not carry any such implication concerning the character of the normal membrane, or the normal parts of the membrane, as does the fact of the complete glomerular filterability of inulin through the entire membrane.

From the facts and considerations which have thus far been presented we conclude that the glomerulus of the amphibian kidney is a filter and not a secreting structure.

How does the volume of glomerular filtrate compare with the volume of urine which the kidney excretes? From a single glomerulus of the exposed kidney of a frog we frequently obtain filtrate at a rate of 1 cmm. per hour. On several occasions collections have been made at rates of from 3 to 4 cmm. per hour. In the normal, wet, unmolested frog we may believe that the filtration rates are higher rather than lower than these. When these rates are used in calculating the total glomerular filtrate formed per hour by the kidneys of a grass frog each of which contains 2000 glomeruli, the estimated filtration rate is from 4 to 16 cc. per hour. The higher

figure is about 8 times as great as the maximum urine output of similar frogs under normal conditions and the lower figure is from 10 to 20 times as great as the urine output of operated frogs.

Is the volume of the glomerular filtrate sufficient to contain all of the substances which the kidney excretes? In our experience, limited in this connection, neutral red is the only substance studied in the renal excretion of which we have been obliged to assume the participation of another mechanism than that of glomerular filtration. From figures for the amount of neutral red excreted per hour, its concentration in the glomerular urine and the number of glomeruli in the kidney it was calculated that from 20 to 57 cmm. of filtrate per glomerulus per hour would have been required to contain the excreted dye. We do not believe that rates as high as these are possible. Hence we conclude that a large fraction of the neutral red was excreted by the tubules. Similar calculations from figures for phenol red indicated that all of this dye which was excreted might have been contained in the glomerular filtrate. These results agree with conclusions drawn from Oliver and Shevsky²⁹ from perfusion experiments.

Similar calculations can be made from data of Marshall and Crane³⁰ concerning the excretion of urea and phenol red in frogs. In the great majority of cases, the calculated rates of filtration were less than 5 cmm. per glomerulus per hour, and hence do not require the assumption that the tubule secretes these substances. Marshall, however, on the basis of high concentration ratios, higher concentration in kidney tissue than in blood and comparisons with the excretion rate of xylose, believes that they are in large part secreted by the frog's tubule. We think that the force of this evidence is far less than that which he has brought forward showing that phenol red is secreted by the tubules of the dog's kidney.³¹

The question may now be asked whether the conclusion, drawn from direct evidence obtained in amphibia, that the glomerular process is solely one of filtration, is applicable to the mammalian kidney, from which as yet no such direct information has been obtained. We believe that it is.

Careful comparisons of structure, made with the aid of modern histologic methods, reveal no difference which suggests that the mammalian glomerulus is a secretory apparatus. On the contrary, the epithelial investment, particularly the epithelial nuclei, are more conspicuous in the glomeruli of amphibia than in those of mammals.

It is unnecessary to review the mass of older evidence, chiefly indirect, which has led the majority of physiologists to accept the filtration doctrine. We wish, however, to add to this evidence some recent observations of our own which have greatly strengthened our conviction in this regard. They concern the excretion of inulin by the dog's kidney.

Inulin has already been described as a polysaccharid of molecular

weight of the order of 3800 to 5000 and presumably of large molecular dimensions. It is not hydrolyzed in the animal body and has been demonstrated to be filterable through the frog's glomerulus. Injected intravenously into a toadfish it is not excreted in the urine, *i. e.*, it is not secreted by the tubule of the aglomerular kidney. The frog's kidney is unable to excrete it when, in a double perfusion experiment, it is contained in the fluid which flows through the intertubular capillaries but not in that flowing through the glomerular capillaries. When injected intravenously into a dog it is excreted quantitatively in the urine with astounding rapidity and often in concentrations amazingly high.³² For example in one dog, 14.5 gm. was injected intravenously. Urine passed in the following 11 minutes contained 5.5 gm. (38% of the injected dose). In the 43 minutes following the end of the injection the kidneys had excreted 10.2 gm. (70%). In several experiments the concentration of inulin in the urine has been found to be as high as 36%.

To prove that this remarkable performance is the result of glomerular filtration solely, it is necessary to show that the tubules of the dog's kidney do not secrete it into their lumina. To get evidence concerning this we have used the classical experiment of Heidenhain which has been one of the chief bulwarks of belief in tubular secretion. A dog's blood pressure was reduced by section of the spinal cord to a level of 30 mm., *i. e.*, a level at which glomerular filtration may be believed to have ceased. Inulin was then injected intravenously. After 20 minutes, during which blood pressure did not rise above 35 mm., the vessels of one kidney were perfused, first with some of the dog's own blood, taken before the inulin injection, in order to wash out the inulin-containing blood, then with warm oxygenated Locke's solution for the few minutes required to get a small amount (0.5 cc.) of urine from its ureter. This urine contained no detectable trace of inulin. Analysis of the cortex of the kidney showed that the concentration of inulin in it was far lower than that in the blood plasma. These results, absence of inulin from urine and low concentration in kidney tissue, give evidence that the low blood pressure prevented glomerular filtration and that no inulin was secreted by the tubules. That the tubules during that period were capable of secreting was shown by the behavior of phenol red which was injected intravenously along with the inulin. The cortex contained the dye in concentration nearly double that of the plasma and the urine obtained by perfusion of the kidney after its excision contained significant amounts.

If the conclusion drawn from these experiments is true, namely, that in the dog the glomerulus is the sole renal pathway of escape of inulin from the blood, it follows from the rapidity with which it is excreted that the volume of the glomerular filtrate is vastly greater than that of the urine which leaves the kidney. In one experiment on a dog weighing 17.5 kg., the volume of glomerular

filtrate calculated from the plasma and urine concentrations and the amount of inulin excreted per minute varied between 84 and 114 cc. per minute. The corresponding rates of urine excretion were 1.8 and 5 cc. per minute. From these figures and Kunkel's estimates of the number of glomeruli in the dog's kidney³³ it was calculated that 5 to 7 cmm. of filtrate per glomerulus per hour were formed. These figures are easily credible when it is recalled that as much as 4 cmm. per hour have been collected from a single frog's glomerulus.

Another substance the excretion of which has long been employed in similar calculations of the rate of glomerular filtration in mammals is creatinin. Rehberg,³⁴ in 1926, accepting Cushny's hypothesis that all of the normal constituents of urine are separated from the blood by glomerular filtration only, chose creatinin, the concentration of which in urine is highest relative to plasma, as the substance whose rate of excretion would most truthfully show the volume of glomerular filtration. If the validity of his assumptions is granted, the amount of creatinin excreted per minute divided by the amount contained in 1 cc. of plasma should give the number of cubic centimeters of glomerular filtrate per minute; and if our conclusion with respect to inulin is correct the results of the calculations from the excretion of creatinin and of inulin should be the same. In a series of experiments with dogs, inulin and creatinin were injected simultaneously.³² Calculations of the glomerular filtration rate from the urine and plasma values of each substance gave approximately the same value. On the average the plasma clearance of inulin was about 10% higher than that of creatinin. The inference from this is that in the dog both inulin and creatinin leave the blood by filtration but that a little creatinin goes back into the blood as the filtrate flows down the tubule.*

In 1932 Jolliffe, Shannon and Smith³⁵ proposed that the plasma clearance of the non-metabolized sugar, xylose, is a more correct measure of glomerular filtration in mammals than that of creatinin. The reasons for the preference lay in the fact that creatinin is excreted by the tubule of the aglomerular fish while xylose is not and in the belief that xylose cannot be reabsorbed from the renal

* Our experiments with inulin were begun in March, 1933, as the result of the desire to find a substance which would not escape from the lumen of the tubule either by active reabsorption or passive diffusion. It soon became obvious that a study of its excretion by mammals might throw light on the question of the indirect measurement of glomerular filtration in mammals and accordingly the experiments with dogs were begun. In October, 1934, we learned that Professor Homer W. Smith and Dr. James F. Shannon had independently inaugurated work with this substance at about the same time and had completed a series of studies more extensive than ours. Their experiments with dogs showed even more consistently than ours that the clearance of inulin is the same as that of creatinin and greater than that of xylose. It is a pleasure to acknowledge the help which we have since received from conversations with Professor Smith and improvements in technique of our experiments which Dr. Shannon assisted us in making. The results which they have obtained in dogs are published in the *American Journal of Physiology*, **112**, 405, 1935.

tubule. Their work with xylose led to the conclusion that a considerable fraction of creatinin is secreted from the blood into the tubule and hence that its excretion does not give a valid measure of glomerular function. Our finding that inulin clearance is the same or greater than that of creatinin and decidedly greater than that of xylose gives reason for belief that xylose is reabsorbed from the tubule; that less of it is excreted by the kidney than is filtered from the blood in the glomeruli.

Study of the excretion of inulin and creatinin by the dog has yielded information which affords an interesting comparison of the function of glomerular capillaries with that of the systemic capillaries. In the experiment cited in which 14.5 gm. of inulin were injected intravenously, 38% of this was excreted in 11 minutes; another 32.5% in the following 32 minutes. Two and four-tenths grams of creatinin were simultaneously injected. Only 16% was excreted in the first 11 minutes, and 17% in the next 32 minutes; yet the plasma was being cleared of the two substances at approximately the same rate. This difference in the rates of actual excretion by the kidney is due to the fact that a much greater fraction of the injected creatinin than of the injected inulin passed out of the blood into the tissues. As has been stated, when a solution of inulin and creatinin is filtered through a collodion membrane with pressure, both substances pass through at the same rate; but when a solution of the two is dialyzed through collodion, it is found that creatinin passes through faster than inulin. From this it is clear that in the dog while inulin and creatinin were passing through the walls of the glomerular capillaries at approximately the same rate in relation to their concentrations in the plasma, creatinin was moving through the walls of the systemic capillaries faster than inulin. This is, of course, what is to be expected if, as we believe, the glomerular process is purely one of filtration while that in the systemic capillaries is a combination of filtration and diffusion.

Changes Which the Glomerular Filtrate Undergoes in Its Passage Through the Tubule.* The methods developed for the collection and analysis of glomerular fluid have proved to be applicable to the study of tubular fluid. Tubules have been punctured at various levels, the sites of puncture being identified either by observation of the kidney during life or after its excision at the end of an experiment. In the latter case the lumen of the punctured tubule was filled with India ink, the kidney immediately excised and dehydrated. After clearing, a scale drawing of the ink-injected tubule was made, and the distances of puncture hole from the ends of the section

* The results outlined in this section have not yet been published in detail. The experiments on the reaction of tubule fluid were made by Drs. Hugh Montgomery and J. A. Pierce; the others were made in collaboration with Drs. C. L. Hudson, T. P. Findley and J. P. Hendrix. Abstracts may be found in the *American Journal of Physiology* (Proceedings), 109, 63, 76, 87, 107, 1934.

of the tubule in which it was found were measured.* Thus, in many experiments the distance within the lumen of the tubule which had been traversed by the fluid before it was collected was accurately known; in the others it was approximately known.

The manipulative difficulties are greater than in glomerular puncture and collection of glomerular urine. This is particularly true in work with the frog's tubule because of its small size, its great tortuosity and because of the difficulty of distinguishing between the proximal and distal convolutions in the living tissue. For this reason the greater number of experiments have been made with *Necturi* in which the tubule is larger and less complex in arrangement.

It was obviously important not to draw fluid into the collecting pipette from parts of the tubule distal to the site of puncture. This mistake was avoided by injecting a globule of mercury or of mineral oil colored with Scharlach R in such a way that the lumen of the tubule was obstructed by it at a point immediately distal to the point of the pipette.

In one group of experiments it was desired to introduce into the tubule an artificial fluid of known composition at one point; take it out for analysis at another. Omission of one plasma constituent from the fluid made it possible to learn whether or not that constituent can come in from the blood; addition of it in excess made it possible to learn whether it was reabsorbed into the blood.

The fashion in which such perfusions of the lumina of single tubules were accomplished can be illustrated by describing the method of perfusing a proximal tubule in *Necturus*. Enough metallic mercury was injected into a renal corpuscle to fill the capsular space, the neck and about 0.5 mm. of the beginning of the proximal tubule. This abolished glomerular filtration. The pipette was then filled with the perfusion fluid and its tip inserted into the lumen of the mercury-filled portion of the tubule. Injection of a little fluid caused the mercury column to break and a globule of mercury to be driven to the distal end where it was arrested by the narrowness of the intermediate section. Injection was interrupted and a second pipette inserted at a point proximal to the mercury blocking the distal end. Fluid from the first pipette was then allowed to flow through the tubule at a slow rate and was collected in the second pipette.

The experiments thus far undertaken concern the reabsorption of water, chlorid and glucose, the change in reaction and changes in the concentrations of inorganic phosphates, urica, uric acid and creatinin. The task has been to measure the changes and to identify the parts of the tubule in which they occur. In every experiment blood was collected at nearly the same time as the tubule fluid and the plasma analyzed along with this. On the basis of the

* These identifications were made by Dr. R. T. Kempton.

analyses of glomerular urine presented above, it is assumed throughout that the concentration of any constituent studied is the same in plasma and in the glomerular filtrate from it. In the accompanying charts the results are plotted as percentage differences between plasma and tubule fluid.

1. *Water*. The discrepancy between the volume of urine which leaves the kidney and the volume of the glomerular filtrate, calculated from the amount of fluid which can be collected from a single glomerulus, is such as to give presumptive evidence of the reabsorption of a large fraction of the glomerular filtrate as it passes through the tubule. More direct evidence of water reabsorption has been obtained by observing the increase in intensity of color which takes place in a phenol red solution injected into and allowed to remain in a single tubule of the frog's kidney. In this experiment the chief site of water reabsorption appeared to be the proximal part of the distal tubule. Some, however, of the water which is reabsorbed passes out through the wall of the proximal tubule. This is shown by the greater difficulty which is encountered in collecting fluid in volume sufficient for analysis from the distal end of the proximal tubule than from the glomerulus or levels of the tubule nearer to it. It is also shown by the observation that when Ringer's fluid was perfused through the lumen of a proximal tubule at a rate and pressure comparable to those of a normal glomerular fluid, the amount collected was significantly less than the amount introduced. Further evidence in this category will be found in the figures for concentration of glucose in fluid collected from proximal tubules of animals poisoned with phlorhizin.

Concerning the possible secretion of fluid into the proximal tubule it can be said as the result of several trials that in *Necturus*, after glomerular filtration had been purposely abolished, attempts to collect fluid from the proximal tubule failed.

2. *Total Concentration; Chlorid Concentration*. The results shown graphically in Figure 2 prove that the activities of the tubule which are responsible for the hypotonicity of amphibian urine and the absence of chlorid from it occur in the distal and not in the proximal tubule. The number and consistency of the results and the fact that they have been obtained with frogs as well as with *Necturi* leave little room for doubt as to the essential correctness of this statement.

It seems necessary to call attention to the difference between this conclusion and that reached by White and Schmitt⁸ from observations made in 1926. By intraeapsular injection they filled the lumen of a tubule of *Necturus* with a suspension of dog's red blood corpuscles stained with methylene blue. The blue stain could be seen in the tubule but no corpuscles could be discerned in it. They expressed the belief that the cells were "almost instantaneously" laked because of reabsorption of chlorid from the

injected fluid and that this must have occurred in the proximal tubule. We are sure that these observations were faulty* and regard it as regrettable that they have been accepted without confirmation by other experimenters.

Perhaps attention should be called also to an apparent inconsistency between our determinations of the total molecular concentration and chlorid concentration in fluid from the proximal tubule. The chlorid concentration seems to be slightly greater, the total concentration slightly less than those of plasma. The inconsistency lies in the fact that chlorid is the predominant factor in the total concentration. At present we can offer no other explanation for this than minor technical imperfections.

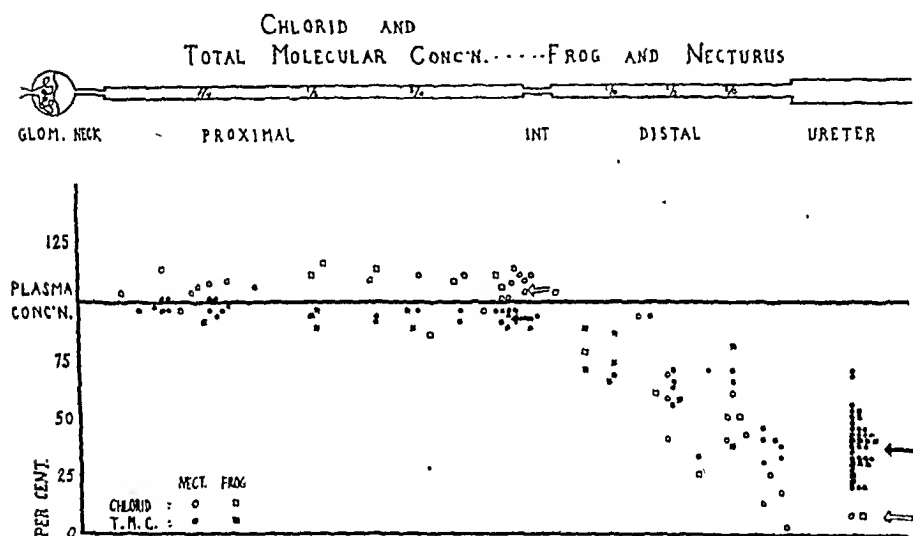


FIG. 2.—Total molecular concentration and chlorid concentration of fluid from the renal tubule. Distances along the abscissa indicate sites of collection. The results are shown as percentage differences from blood plasma. Arrows represent averages.

3. *The Reaction of Tubule Fluid.* Figure 3 shows the results of experiments by Drs. Montgomery and Pierce in which the pH of tubular fluid was determined by means of a microquinhydrone electrode.³⁶ It is clear that no significant change in reaction of the fluid occurs during passage through the proximal tubule; acidification, presumed to be due to reabsorption of bicarbonate, takes place exclusively in the distal tubule. This confirms a less precise observation made several years ago in which a phenol red solution introduced into a frog's tubule, was seen to change in color from red to yellow only after it had passed into the distal third of the entire tubule.

* Since this was written we have made careful repetitions of the experiments by White and Schmitt. The observations, which will be published elsewhere in detail, completely fail to agree with theirs.

4. *Glucose*. Figure 4 shows the concentrations of reducing substances in fluid taken from various levels of the tubule. Glomerular fluid contains glucose in the same concentration as plasma. No

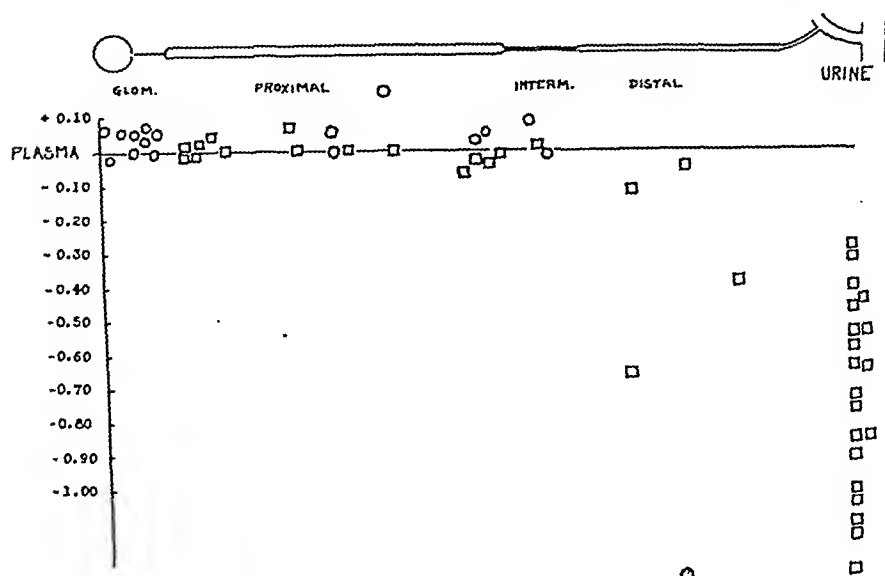


FIG. 3.—pH determinations of fluid from the renal tubule, shown as differences from those of plasma.

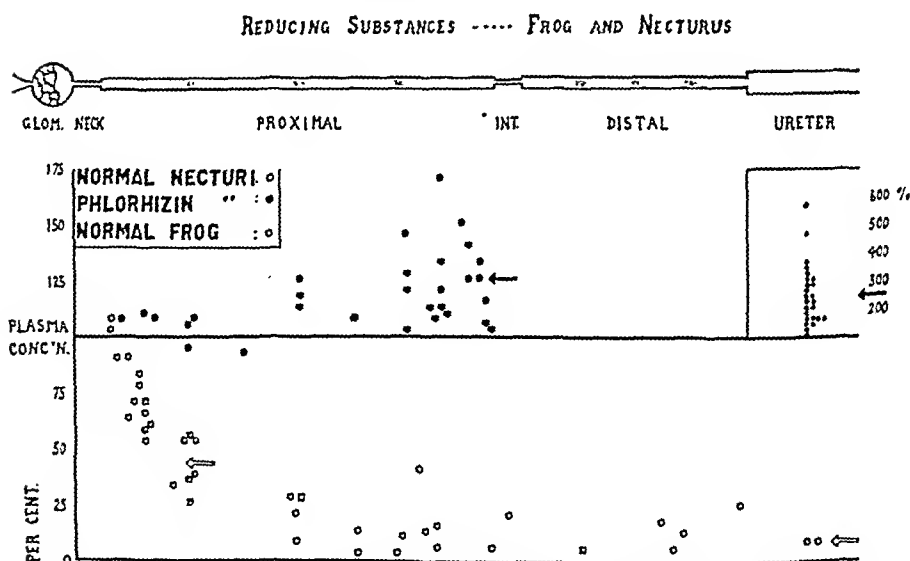


FIG. 4.—Reducing substances in fluid from the renal tubules shown as percentage differences from plasma. Open circles, normal Neeturi; open squares, normal frogs; black circles, phlorhizinized Neeturi. Arrows represent averages.

change occurs in passing through the neck of the tubule; the concentration diminishes rapidly as flow through the proximal tubule proceeds. When half of its length has been traversed the concen-

tration may be as low as it is in ureteral urine. The capacity of mediating the selective reabsorption of glucose is not however limited to the proximal half of the proximal tubule; for when Ringer's solution containing glucose is slowly perfused through the distal half of the proximal, the sugar disappears from it. When, however, a glucose solution is perfused through the distal tubule its concentration remains the same or increases. The sole site of selective glucose reabsorption, therefore, is the proximal tubule.

In Figure 4 is also shown a series of results which were obtained by analyzing tubule fluid from animals poisoned with phlorhizin. Since it is known that phlorhizin does not affect the glomerular filtration of glucose,¹⁷ the meaning of these results is unmistakable. The action of phlorhizin on the kidney which results in glycosuria consists in abolition of the capacity of the cells of the proximal convoluted tubule to effect the selective reabsorption of glucose. This statement which agrees with current belief is based upon evidence more direct than that previously available.

The further question arose whether during the action of phlorhizin glucose, having reached a concentration in the tubule higher than that in the blood, can diffuse from the tubule into the blood. Does phlorhizin prevent passive diffusion as well as active reabsorption of glucose from the tubule? The question is important, for if it does, then the assumption, made by some workers in this field, that in phlorhizin poisoning *all* of the glucose contained in the glomerular filtrate leaves the kidney through the ureter is justified; and in that event the plasma clearance of glucose can be rightly accepted as a measure of the volume of glomerular filtration.

An answer to this question was obtained by perfusing, through the lumen of a proximal tubule of *Necturus*, Ringer's solution containing glucose in higher concentration than that in the blood plasma. The concentration in the recovered fluid was from 15 to 40% less than in the original fluid. Phlorhizin, therefore, does not prevent the escape of glucose from the renal tubule by diffusion.

A related question was studied, which concerns the behavior of xylose in the tubule. It was discovered by Jolliffe, Shannon and Smith³⁵ that the plasma clearance of xylose in the normal dog is the same as the glucose clearance in the dog poisoned by phlorhizin; and xylose clearance has come to be adopted by some investigators as a measure of glomerular filtration in normal animals. But when xylose solutions were perfused through the proximal tubules of frogs and *Necturi* the xylose concentrations decreased by 13 to 73%. Since these results cannot be explained by entrance of water into the tubule, we have confidence in saying that in a phlorhizinized tubule of *Necturus*, when the glucose concentration of the fluid passing through it reaches a certain excess over that of the blood, glucose diffuses back into the blood; and that in normal amphibia, xylose is capable of escaping from the tubule through

its wall. These conclusions are in harmony with those drawn from the study of the excretion of inulin by the dog.

The results obtained in the study of the change in the concentration of glucose which proceeds in the proximal tubules of phlorhizinized animals give strong evidence that the proximal tubule is the site of some of the water reabsorption. On the average, glucose is 26% more concentrated in the fluid which leaves the proximal tubule than in that which enters it. We know of no evidence which shows that the phlorhizinized tubule secretes glucose; much that it does not. Relying on this, we conclude that the increase in glucose concentration in the proximal tubule fluid is the result of an active reabsorption of water which amounts on the average to at least 20% of the volume of the glomerular filtrate.

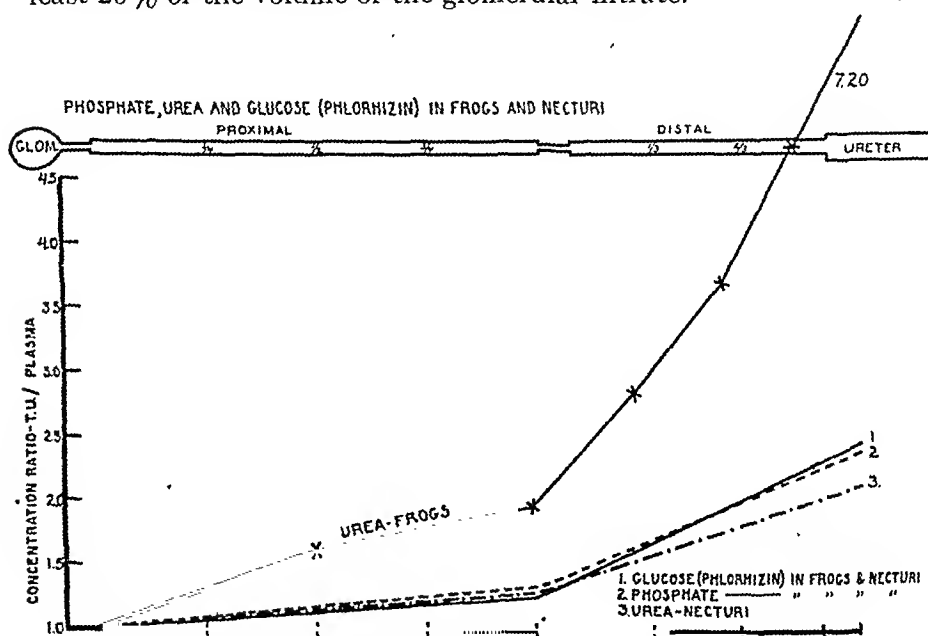


FIG. 5.—Average curves of analyses of tubule fluid for glucose in phlorhizin poisoning and urea and inorganic phosphates in normal animals.

Inorganic Phosphate, Urea, Uric Acid, Creatinin. Thus far we have discussed the functions of the tubule only in relation to substances which are reabsorbed in their passage through it: water, chlorid, bicarbonate, glucose. Something must now be said concerning the behavior of substances which are excreted in the urine in higher concentration than that in which they exist in plasma and in the glomerular filtrate. In this category we have studied inorganic phosphate, urea, uric acid and creatinin.

Figure 5 contains curves, each the composite of many experiments, which show the average changes in concentration which phosphate and urea undergo in their passage through the tubule.

Included also is the average curve which represents the increase in concentration which glucose undergoes in the phlorhizinized tubule. If, as we believe, this is the result of reabsorption of water it follows that similar change in concentration of another substance is similarly explainable.

Inorganic phosphate in both frogs and *Necturi* and urea in *Necturi* undergo, on the average, degrees of concentration so similar to that of glucose in phlorhizin poisoning that one explanation is adequate for all, namely, reabsorption of water. We see no necessity for assuming that in these experiments active secretion of phosphates was a factor. The case is different, however, with urea in the frog's tubule. It is possible, though not necessarily certain, that the concentration at the end of the proximal tubule (double that of glomerular fluid) cannot be explained by water reabsorption but that some urea was secreted. The most striking feature of the urea curve, however, is the steep rise in concentration which takes place in the distal tubule. The average concentration ratio attained (7.2) is derived from figures which go as high as 20. If secretion of urea is a factor in the production of these high concentrations the suspicion is aroused that the distal tubule is its chief site. What is urgently needed in further experiments of this sort is some more conclusive method of measuring the absorption of water from the tubule.

In studying the changes in concentration which uric acid and creatinin of the glomerular filtrate undergo in passing through the tubule, it was necessary to inject both substances before beginning an experiment because of the small amounts normally present in the blood. In frogs the changes in uric acid were similar to, though not so pronounced as those of urea; in *Necturi* its concentration may increase slightly or may decrease during passage through the tubule. The results give no reason to think that it is secreted by the tubule of *Necturus*; we are uncertain about the frog's tubule.

Creatinin in the frog's tubule behaved like uric acid in *Necturus*; there was no increase in concentration sufficient to suggest secretion; often there was a decrease. In a few experiments with *Necturus*, however, creatinin became more concentrated in the proximal tubule than any other substance yet studied by these methods. It may well be that this is indicative of a secretory process for creatinin operative in the proximal tubule of *Necturus*, not in that of the frog.

The most striking outcome of these experiments, aside from the scanty evidence they afford of the existence of secretory processes in the epithelium of the proximal tubule, is the demonstration of radical differences in the behavior of urea, uric acid and creatinin in the tubules of the two species studied. Results obtained with one are definitely not transferable to the other. Obviously it would

be even more hazardous to draw conclusions concerning secretion by the mammalian tubule from these results.

We have hope and some expectation that the methods which have been developed in these studies will be found applicable to the mammalian kidney. It seems not unreasonable to anticipate that when that objective is attained it will be found that the reabsorptive processes, so conspicuously apparent and definitely localizable in the amphibian tubule and so fundamentally important for survival, will be found in the analogous sections of the tubule of the mammal.

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(Titles have been omitted for the sake of brevity.)

THE URINARY CONCENTRATION IN DIABETES INSIPIDUS.

A COMPARISON OF THE EFFECTS OF SEVERAL DRUGS.

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MANY drugs have been studied and recommended in the therapy of diabetes insipidus, but, at present, derivatives of the posterior lobe of the pituitary gland have largely replaced all others. The work of Scherf,¹ however, has recently aroused interest in amidopyrin, and Kahn² has reported a case successfully treated by this substance. F. M. Smith³ has called attention to the economic aspect of treatment and has shown that the insufflation of powdered posterior pituitary substance is just as efficient and far cheaper than the usual extracts given subcutaneously. Smith's observations have been confirmed by Canelo and Lissner.¹⁰

It seemed desirable, therefore, to attempt to compare the effect of some of these drugs on the urinary concentration. Two cases of diabetes insipidus fortunately became available for this work.

Methods. During the periods of study the patients were confined to bed and the utmost precautions were taken not to suggest the outcome of tests or therapy. When a drug was to be tried, a control period was used during which a suitable placebo was administered. They were invariably able to distinguish the potent drugs by the effect on thirst and diuresis.

A standard test was devised to study the effect of various drugs on urinary concentration. It seemed desirable to eliminate the factor of thirst. A typical test period ran for 48 hours, starting at 6 A.M. At that time, and at 2-hour intervals, the patient drank 500 cc. of water and emptied the bladder. She was awakened at night for this purpose. The placebo, in the form of tablets, capsules or hypodermic injections of distilled water, was given at 10 A.M. of the first day and the trial drug was given at the same time the next day. During the 2 days, 6 identical meals were served to control the water and chlorid intake from that source. The 2-hour urine specimens were examined for color, the volume was measured, and the specific gravity determined with the urinometer.

The specific gravity of the urine was taken as an indication of the concentration of dissolved solids in the urine.^{4,5} While diminution in volume output during the 2-hour periods was noted, and corresponded fairly well with increased specific gravity, yet volume output as measured in these tests is subject to variation from other factors, such as the voluntary control of the bladder

and variations in water balance which may have no apparent relation to the problem at hand. It would therefore appear that increase in the specific gravity of the urine seems to be a more accurate index of the potency of antidiuretic drugs in diabetes insipidus.

Case Reports. CASE 1.—L. O., housewife, aged 42, was under observation from July, 1933, to March, 1934. She had apparently been in good health until October, 1921, when polydipsia and polyuria first occurred. Several months later she was studied in a private hospital, where her urinary output averaged 16 quarts (15 liters) in 24 hours. The diagnosis of diabetes insipidus was made then. Since that time the diuresis had been continuous but the daily output had gradually diminished. Among her numerous complaints were pain in the hips, headache, emotional instability, transient paralyses, and "fainting spells." She had been a semi-invalid for the last year because of fear of falling. The previous medical history was not significant except that she had given birth to a child precipitately 9 months before the onset of the diuresis.

Physical examination revealed no abnormalities except a moderately enlarged heart. She weighed 145 pounds and was 61 inches tall. Repeated neurologic examinations were negative. The neurologists were forced to explain her many complaints on the basis of hysteria. The ocular fundi were normal and the visual fields were not impaired. No remnants of Rathke's pouch were found. Teleoroentgenogram gave a Danzer ratio of 0.57. Electrocardiogram showed slight left axis deviation. The basal metabolic rate was -6%. Blood counts were normal. Blood Kahn and Wassermann tests were negative. Blood urea, uric acid, creatinin, calcium and phosphorus determinations were repeatedly normal.

When she was allowed to drink freely, the average fluid intake in 24 hours, excluding water in the food, was 6430 cc. and the urinary output was 5672 cc. The daily (6 A.M. to 6 P.M.) intake slightly exceeded the night intake, whereas the nocturnal output was usually greater than the diurnal. The urine was examined frequently but no casts or cellular elements were ever found in excess. Glucose and albumin were never noted. The specific gravity never exceeded 1.004 except when specific medication was given.

Results. The drugs studied were amidopyrin (Pyramidon), acetyl salicylic acid (aspirin), antipyrin, acetphenetidin (phenacetin), vasopressor fraction of posterior pituitary gland (pitressin—Parke, Davis & Co.), histamin, morphin sulphate, sodium bromid and powdered posterior pituitary substance (Eli Lilly & Co.).

During the control periods of the tests the specific gravity of the urine never exceeded 1.004, while the 2-hourly fluid output varied between 240 cc. and 870 cc. with an average of around 500 cc. Some of the variation between the volumes of different specimens may be accounted for by the fact that the capacity of the bladder was found to be 1400 cc. and it may not have been possible to empty it completely each time. There was no constant change in urinary volume or specific gravity which could be ascribed to the ingestion of food.

Posterior Pituitary Gland. Two substances were studied: The vasopressor fraction known as "pitressin" (Parke, Davis & Co.), and a powdered preparation of the posterior lobe (Eli Lilly & Co.),

TABLE 1 (CASE 1).—PITRESSIN.

Date, 1933.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
December 11	6 A.M.—8 A.M.	500	660	1.001	7 A.M. meal.
	8 "—10 "	"	580	1.002	
	10 "—12 M.	"	560	1.003	10 A.M. <i>sterile water</i> (hypo).
	12 M.—2 P.M.	"	420	1.003	12 M. meal.
	2 P.M.—4 "	"	540	1.004	
	4 "—6 "	"	440	1.004	5:30 P.M. meal.
	6 "—8 "	"	520	1.004	
	8 "—10 "	"	820	1.003	
	10 "—12 "	"	340	1.003	
	12 "—2 A.M.	"	780	1.003	
December 12	2 A.M.—4 "	"	410	1.003	
	4 "—6 "	"	640	1.003	
	6 "—8 "	"	330	1.003	7 A.M. meal.
	8 "—10 "	"	810	1.003	
		Total	Total		
		7000	7850		
	10 A.M.—12 M.	500	240	1.006	10 A.M. 1 cc. <i>pitressin</i> (hypo).
	12 M.—2 P.M.	"	100	1.015	12 M. meal.
	2 P.M.—4 "	"	100	1.015	
	4 "—6 "	"	110	1.010	5:30 P.M. meal.
December 13	6 "—8 "	"	150	1.012	
	8 "—10 "	"	270	1.006	
	10 "—12 "	"	300	1.006	
	12 "—2 A.M.	"	220	1.005	
	2 A.M.—4 "	"	490	1.004	
	4 "—6 "	"	430	1.003	
		Total	Total		
		5000	2410		
	6 A.M.—8 A.M.	400	580	1.004	7 A.M. meal.
	8 "—10 "	200	540	1.003	
December 14	10 "—12 M.	400	670	1.003	
	12 M.—2 P.M.	200	490	1.000	12 M. meal.
	2 P.M.—4 "	400	550	1.003	
	4 "—6 "	400	430	1.004	5:30 P.M. meal.
	6 "—8 "	400	450	1.004	
	8 "—10 "	200	450	1.000	
	10 "—12 "	200	410	1.002	
	12 "—2 A.M.	200	360	1.004	
	2 A.M.—4 "	200	270	1.002	
	4 "—6 "	200	610	1.003	
		Total	Total		
		3400	5810		
		Grand total	Grand total		
		15,400	16,070		

representing 5 times the weight of the wet gland. Attention has been called to the latter substance by F. M. Smith.³

Table 1 shows the effect of 1 cc. pitressin hypodermically upon the volume output and the specific gravity of the urine. During the first 2-hour period the volume was 240 cc. and specific gravity 1.006. In the next period the volume was reduced to 100 cc. and the specific gravity was 1.015. The effect of the dose is seen to last from 10 A.M. to 2 A.M. (16 hours) with the maximum effect from 2 to 6 hours after administration. During the time when this drug was acting, the patient was drinking 500 cc. of water every 2 hours and urinating only 20 to 30% of it. Twenty hours after injection the patient had drunk 5000 cc. of water and excreted only 2410 cc., withholding 2590 cc. In a supplementary 24-hour period she was allowed to drink as much as desired and her output finally exceeded her intake. This supplementary period was not repeated in subsequent tests.

TABLE 2 (CASE 1).—POWDERED POSTERIOR PITUITARY SUBSTANCE.

Date, 1934.	Time	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
March 13	6 A.M.—8 A.M.	500	330	1.002	7 A.M. meal.
	8 "—10 "	"	50	1.028	8 A.M. 0.05 gm. powdered posterior pituitary in nose.
	10 "—12 M.	"	120	1.012	
	12 M.—2 P.M.	"	100	1.010	12 M. 0.05 gm. powdered posterior pituitary in nose.
	2 P.M.—4 "	"	60	1.028	12 M. meal.
	4 "—6 "	"	110	1.020	4 P.M. 0.05 gm. powdered posterior pituitary in nose.
	6 "—8 "	"	120	1.016	5:30 P.M. meal.
	8 "—10 "	"	400	1.006	
	10 "—12 "	"	610	1.004	
	12 "—2 A.M.	"	530	1.003	
March 14	2 A.M.—4 "	"	800	1.002	
	4 "—6 "	"	850	1.001	
	6 "—8 "	"	500	1.001	7 A.M. meal.
March 15	8 "—10 "	"	470	1.003	8 A.M. 0.05 gm. powdered posterior pituitary under tongue.
	10 "—12 M.	"	640	1.002	
	12 M.—2 P.M.	"	430	1.003	12 M. meal.
	2 P.M.—4 "	"	830	1.002	
	4 "—6 "	"	470	1.003	4 P.M. 0.1 gm. powdered posterior pituitary by mouth.
	6 "—8 "	"	470	1.000	5:30 P.M. meal.
	8 "—10 "	"	710	1.001	
	10 "—12 "	"	660	1.001	
March 16	12 "—2 A.M.	"	670	1.002	
	2 A.M.—4 "	"	540	1.001	
	4 "—6 "	"	660	1.001	

Table 2 shows the results of the administration of powdered posterior pituitary substance intranasally, under the tongue, and orally. The 2-hour output of urine was reduced to 50 or 60 cc. and the specific gravity was raised to 1.028 on 2 occasions by the administration of 50 mg. of the powder in the nose. Fifty milli-

grams of the powder had no effect under the tongue and 100 mg. by mouth 4 hours after a meal were likewise ineffectual.

For nasal administration single doses of the powder were weighed out into papers and the dose taken up in a dry medicine dropper and insufflated well into the nares. The patient was sent home at one time with instructions to take 50 mg. of the powdered substance intranasally 3 times daily. The drug was very effective but the patient complained that the nasal mucosa became painful and that the powder tended to form crusts in the nares.

Each of the following drugs was administered in the course of a separate 48-hour test period, exactly duplicating the first 48 hours outlined for pitressin.

TABLE 3 (CASE 1).—AMIDOPYRIN.

Date. 1933.	Time.	Vol- ume in- take, cc.	Urine.		All meals identical in composition.
			Vol- ume, cc.	Specific gravity.	
November 1	6 A.M.—8 A.M.	500	420	1.001	7 A.M. meal.
	8 "—10 "	"	480	1.002	
	10 "—12 M.	"	670	1.002	10 A.M. placebo tablets.
	12 M.—2 P.M.	"	350	1.004	12 M. meal.
	2 P.M.—4 "	"	410	1.003	
	4 "—6 "	"	420	1.004	5:30 P.M. meal.
	6 "—8 "	"	410	1.004	
	8 "—10 "	"	510	1.001	
	10 "—12 "	"	430	1.003	
	12 "—2 A.M.	"	290	1.003	
November 2	2 A.M.—4 "	"	610	1.003	
	4 "—6 "	"	590	1.002	
	6 "—8 "	"	360	1.000	7 A.M. meal.
	8 "—10 "	"	640	1.003	
	10 "—12 M.	"	130	1.007	10 A.M. 2 gm. amidopyrin by mouth. Urine pink.
	12 M.—2 P.M.	"	80	1.011	12 M. meal. Urine orange.
	2 P.M.—4 "	"	210	1.005	Urine pink.
	4 "—6 "	"	280	1.005	5:30 P.M. meal. Urine pink.
	6 "—8 "	"	430	1.004	Urine pink.
	8 "—10 "	"	190	1.003	Urine pink.
November 3	10 "—12 "	"	70	1.004	Urine pink.
	12 "—2 A.M.	"	350	1.004	Urine reddish.
	2 A.M.—4 "	"	280	1.001	Urine pink.
	4 "—6 "	"	600	1.003	Urine pink.

Amidopyrin. The use of this drug was suggested by Scherf.¹ Table 3 shows the effect of the ingestion of 2 gm. In the second 2-hour period the urinary output was only 80 cc. and the specific gravity 1.011. The effect lasted about 8 hours in all, but the maximum was from 2 to 4 hours. The urine was colored orange by the drug and some trace of color was seen as long as 18 hours after administration of the single dose.

During several weeks in the hospital the diuresis was controlled to the patient's satisfaction, at least, by the oral administration of

1 gm. of amidopyrin before retiring. Whereas she usually awoke 5 or 6 times to void, she was enabled to sleep through the night, arising only once or not at all. In comparing day and night specimens it was rather puzzling to note that the nocturnal output was not much decreased in spite of the patient's observations. The urologist found that the capacity of her bladder was 1400 cc., and while the specific gravity of the night urine was somewhat higher than the diurnal, yet it is possible that the drug also tended to diminish the irritability of the bladder. The patient also reported that her thirst was much relieved. In spite of our objective evidence that the intranasal pituitary powder was much more effective, she voluntarily reverted to the use of amidopyrin while at home because of the local irritation caused by the powder.

Neutropen did not have a marked effect on administration of the drug for several months.

Sodium Bromide. The drug administered by mouth produced no effect on the concentration or volume output in a standard 48-hour test.

Morphine. The drug administered in 10th gram morphin sulphate subcutaneous injections had no effect by a 48-hour test period.

Histamine. The drug was not used because Gibson and Martin⁶ reported marked diuresis in the rat. In our case 0.003 gm. was given subcutaneous. In the typical headache and peripheral vasodilation which followed, there was no effect on the specific gravity of the urine. It is possible, however, that in collecting 2-hour specimens the diuretic effect may have been masked.

Acetyl Salicylic Acid. The drug had no effect in a standardized test after the ingestion of 10 gm. of the drug. The urine was colored brown for 4 hours after ingestion.

Acetyl Salicylic Acid. The administration of 2 gm. by mouth caused a decrease in the urinary specific gravity to 1.006 in the period 2 hours after ingestion. The 2-hour output was 290 cc.

Antipyrin. Two grams of the drug by mouth caused the 2-hour urinary outputs to be reduced to 210 cc. and 150 cc. for the 2 periods following administration. The specific gravities for the 2 periods were 1.006 and 1.009 respectively. Eichhorst,⁷ in 1888, reported that this drug effectively controlled the diuresis.

CASE 2. - A D., housewife, aged 56, was studied in the University Hospital from January 5 to February 21, 1935. She had had polydipsia and polyuria for about 1 year, the symptoms increasing in severity 5 months before admission. She had lost 20 pounds in weight associated with anorexia. For 6 months she had noted a mass in the lower abdomen which had slowly increased in size.

She was apparently quite weak and undernourished. The skin was dry and rough. The abdomen was distorted by a globular tumor arising from the pelvis and extending nearly to the umbilicus. The cervix uteri appeared normal and the tumor appeared to be associated with the fundus uteri.

Blood counts showed a slight secondary anemia. Basal metabolic rate was +9%. The visual fields were not impaired. Roentgenologic studies of the skull, chest and gastro-intestinal tract revealed no abnormalities.

During a 5-day period she drank fluids *ad libitum* and the average 24-hour urinary volume was 6120 cc. The maximum specific gravity of these specimens was 1.002. A series of concentration tests previously described in Case 1 was then employed. She was then transferred to the Department of Gynecology, where surgical exploration was performed. The tumor mass was found to be an adenocarcinoma of both ovaries and endometrium (Krukenberg type). There was an area of induration in the stomach which was thought to be a possible primary focus. There was no evidence of other metastases and no involvement of the nerve supply to the kidneys.

For 10 days postoperation the 24-hour urinary output averaged 1200 cc., although fluids were not restricted. This was thought to be due to the lumbar puncture by which anesthesia had been obtained. After this period, diuresis was controlled by 50 mg. powdered posterior pituitary substance intranasally at 7 A.M. and 7 P.M.

She received deep Roentgen ray therapy and was sent home, where she died March 2, 1935. No autopsy was performed.

Results. The effect of 4 drugs on the urinary concentration was studied by means of the standardized test devised.

Pitressin. One cubic centimeter of pitressin (hypo) only concentrated the urine to a specific gravity of 1.008. The minimum 2-hourly output during this test was 90 cc. Details are set forth in Table 4.

TABLE 4 (CASE 2).—PITRESSIN.

Date, 1935.	Time.	Vol- ume in- take, cc.	Urine.		All meals identical in composition.
			Vol- ume, cc.	Specific gravity.	
January 13	6 A.M.—8 A.M.	500	640	1.000	7 A.M. meal.
	8 "—10 "	"	720	1.001	
	10 "—12 M.	"	680	1.003	10 A.M. sterile water (hypo).
	12 M.—2 P.M.	"	660	1.003	12 M. meal.
	2 P.M.—4 "	"	790	1.001	
	4 "—6 "	"	430	1.003	5:30 P.M. meal.
	6 "—8 "	"	660	1.002	
	8 "—10 "	"	660	1.001	
	10 "—12 "	"	470	1.004	
	12 "—2 A.M.	"	610	1.003	
January 14	2 A.M.—4 "	"	390	1.001	
	4 "—6 "	"	560	1.003	
	6 "—8 "	"	460	1.003	7 A.M. meal.
	8 "—10 "	"	440	1.003	
	10 "—12 M.	"	90	1.005	10 A.M. 1 cc. pitressin (hypo).
	12 M.—2 P.M.	"	130	1.008	12 M. meal.
	2 P.M.—4 "	"	190	1.008	
	4 "—6 "	"	150	1.003	5:30 P.M. meal.
	6 "—8 "	"	300	1.004	
	8 "—10 "	"	310	1.004	
January 15	10 "—12 "	"	170	1.005	
	12 "—2 A.M.	"	150	1.006	
	2 A.M.—4 "	"	110	1.003	
	4 "—6 "	"	260	1.000	

Powdered Posterior Pituitary Substance (Table 5). A single 50 mg. dose in the nose induced a maximum specific gravity of the urine of 1.017. The minimum volume output for 2 hours was 18 cc.

TABLE 5 (CASE 2).—POWDERED POSTERIOR PITUITARY SUBSTANCE.

Date, 1935.	Time.	Vol- ume in- take, cc.	Urine.		All meals identical in composition.
			Vol- ume, cc.	Specific gravity.	
January 16	6 A.M.—8 A.M.	500	630	1.002	7 A.M. meal.
	8 "—10 "	"	570	1.003	
	10 "—12 M.	"	180	1.009	10 A.M. 0.05 gm. powdered posterior pituitary substance nasally.
	12 M.—2 P.M.	"	18	1.014	12 M. meal.
	2 P.M.—4 "	"	45	1.016	
	4 "—6 "	"	80	1.017	5:30 P.M. meal.
	6 "—8 "	"	65	1.017	
	8 "—10 "	"	430	1.004	
	10 "—12 "	"	420	1.004	
	12 "—2 A.M.	"	300	1.002	
January 17	2 A.M.—4 "	"	340	1.003	
	4 "—6 "	"	430	1.001	

TABLE 6 (CASE 2).—AMIDOPYRIN.

Date, 1935.	Time.	Vol- ume in- take, cc.	Urine		All meals identical in composition.
			Vol- ume, cc.	Specific gravity	
January 18	6 A.M.—8 A.M.	500	610	1.001	7 A.M. meal.
	8 "—10 "	"	660	1.001	
	10 "—12 M.	"	320	1.003	10 A.M. 2 gm. amidopyrin by mouth. Urine pink.
	12 M.—2 P.M.	"	190	1.005	12 M. meal. Urine pink.
	2 P.M.—4 "	"	22	1.005	Urine pink.
	4 "—6 "	"	100	1.007	5:30 P.M. meal. Urine orange.
	6 "—8 "	"	90	1.010	Urine red.
	8 "—10 "	"	100	1.007	Urine red.
	10 "—12 "	"	80	1.009	Urine red.
	12 "—2 A.M.	"	40	1.011	Urine orange.
January 19	2 A.M.—4 "	"	70	1.012	Urine pink.
	4 "—6 "	"	170	1.007	Urine pink.

Amidopyrin (Table 6). Two grams by mouth caused a maximum specific gravity of 1.012 and a minimum 2-hour output of 22 cc. For some undetermined cause the action of this drug was much prolonged in Case 2.

Obstetrical Pituitrin (Table 7). One cubic centimeter of this drug hypodermically produced a slight concentration in the urine (specific gravity 1.005).

TABLE 7 (CASE 2).—PITUITRIN.

Date, 1935.	Time.	Vol- ume in- take, cc.	Urine.		All meals identical in composition.
			Vol- ume, cc.	Specific gravity.	
January 20	6 A.M.—8 A.M.	500	690	1.000	7 A.M. meal.
	8 "—10 "	"	720	1.002	
	10 "—12 M.	"	200	1.005	10 A.M. 1 cc. <i>obstetrical pituitrin</i> (<i>hypo</i>).
	12 M.—2 P.M.	"	270	1.005	12 M. meal.
	2 P.M.—4 "	"	360	1.003	
	4 "—6 "	"	430	1.004	5:30 P.M. meal.
	6 "—8 "	"	470	1.003	
	8 "—10 "	"	460	1.003	
	10 "—12 "	"	320	1.003	
	12 "—2 A.M.	"	430	1.003	
January 21	2 A.M.—4 "	"	270	1.002	
	4 "—6 "	"	260	1.003	

Summary. Two cases of diabetes insipidus of unknown etiology have been studied with reference to the effect of various drugs on the concentration of the urine.

A test has been devised which allows an evaluation and comparison of the effect of drugs on the urinary concentration. This test eliminates the factor of thirst from consideration.

If the maximum specific gravity of a 2-hour urine specimen obtained under conditions of the test be taken as an index of the effect of the drug in Case 1, the drugs can be ranged in the following order of potency:

	Specific gravity.
0.05 gm. powdered posterior pituitary substance (intranasally)	1.028
1 cc. pitressin (hypodermically)	1.015
2 gm. amidopyrin (orally)	1.011
2 gm. antipyrin (orally)	1.009
2 gm. acetyl salicylic acid (orally)	1.006
2 gm. acetphenetidin (orally)	No effect
2 gm. sodium bromid (orally)	No effect
0.003 gm. histamin (hypodermically)	No effect
0.01 gm. morphin sulphate (hypodermically)	No effect

In Case 2 a similar comparison can be made:

	Specific gravity.
0.05 gm. powdered posterior pituitary substance (intranasally)	1.017
2 gm. amidopyrin (orally)	1.012
1 cc. pitressin (hypodermically)	1.008
1 cc. obstetrical pituitrin (hypodermically)	1.005

These results supplement the studies of F. M. Smith³ and Vidgoff⁸ on the effects of the nasal insufflation of powdered posterior pituitary substance. In Smith's experiments the possibility of some effect of the drug on thirst was not eliminated. The tests confirm Eichhorst's

report⁷ on the efficacy of antipyrin. The reports of Scherf¹ and Kahn² as to the value of amidopyrin are also confirmed. In view of the recent reports of the occurrence of agranulocytosis following administration of amidopyrin,⁹ this drug should be used with caution.

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THE NATURE OF OSTEOGENESIS IMPERFECTA.*

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THE purpose of this report is to present the results of an extensive clinical investigation of a typical case of *osteogenesis imperfecta*.

Armand¹ reported as early as 1716 a case of this disease. A thorough clinical and probably the first anatomic description was made by v. Lobstein² in 1833. The term "Lobstein's disease" is still encountered. He applied the name "idiopathic osteopsathyrosis." Henzschel³ noted the blue scleræ in 1831. In 1848, the blue scleræ and multiple fractures were associated with this disease by Cornaz.⁴

The china or slate-blue scleræ are characteristic. Their color

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is due to partial visibility of the underlying choroid. The bone fragility is so increased that even slight trauma may produce fractures. Fractures occur from the intrauterine period to advanced age, are most common in infancy and early youth, and decrease at puberty. They occur almost exclusively in the shafts of the long bones and in the ribs. There is little or no associated pain, and the bones usually heal rapidly.

Deafness, associated with otosclerosis,⁵ usually occurs in the second decade. It accompanies the blue scleræ and brittle bones in 40% of the cases.⁵ Heredity was a factor in 28% of the cases collected by Fairbank.⁶

The pathologic findings are presented in the excellent monograph of Key.⁷ Necropsy has revealed no major pathologic process save in the bones.⁸ A decrease in osteoblasts and a defective production of osteoid tissue have been noted.^{9,10}

The etiology is obscure. Some investigators suspect a faulty metabolism resulting from various endocrine disturbances. On the other hand, the endocrine glands have been found normal at necropsy by Kraus¹¹ and recently by Hennessy.¹² The calcium and phosphorus content of the affected bones are normal.^{13,14} The serum calcium and phosphorus, as well as the calcium balance, remain within normal range, as revealed by the data we are about to report, and by Hunter's^{15,16} and Klercker's¹⁷ investigations. The thymus has been suspected. Gorter, quoted by Fairbank,⁶ and Ryan¹⁸ reported improvement subsequent to the administration of thymus. Metabolic studies, however, were not made.

Others consider a developmental anomaly of the mesoblast. Bauer⁹ was one of the first to advocate this theory. He suggested a deficiency of all mesenchymal tissues and showed histologic abnormalities in bone, cartilage and tooth pulp. Key⁷ regards the blue scleræ as evidence of an hereditary hypoplasia of the mesenchyma.

The disease may be due to a deficiency in phosphatase production. This "splitting enzyme" was described by Robison¹⁹ in 1923. It is most plentiful in ossifying portions of normal bone. Robison's theory¹⁹ has received support in the work of Kay,²⁰ who finds that the osteoblasts and hypertrophied cartilage cells secrete this enzyme. Crooks²¹ reported in one instance an increased plasma phosphatase. The bone phosphatase in this disease has not been investigated, so far as we are aware.

Recently we have had the opportunity of investigating a typical instance of *osteogenesis imperfecta*. We were particularly interested in determining any relationship to hyperparathyroidism.

Case Report. B. N., No. 335288, a white male, aged 17, who was referred by Dr. P. L. Ring, Bellaire, Ohio, entered this hospital complaining of a multiplicity of painless fractures. His mother, who volunteered the following information, stated that although his delivery was normal, there

was at the time of birth, an abnormal contour of the right arm and left leg and slate-blue scleræ. About a week later it was learned that these deformities were due to fractures. Since that time he has sustained 48 fractures, all of which have involved the long bones and ribs, 40 occurring before the age of 11. Since then fractures have occurred with decreasing frequency. These fractures were accompanied by little or no pain, were easily reduced and readily healed by immobilization. There is no history of non-union and at no time was open reduction necessary. Occasionally there was mild discomfort but this disappeared in about 2 or 3 days. He became aware of his susceptibility to fractures and therefore avoided any trauma or sudden motion such as twisting or turning. Numerous Roentgenograms have been taken throughout his life. These revealed a "type of osteoporosis." His deciduous teeth were lost early. Many were lost while chewing food.

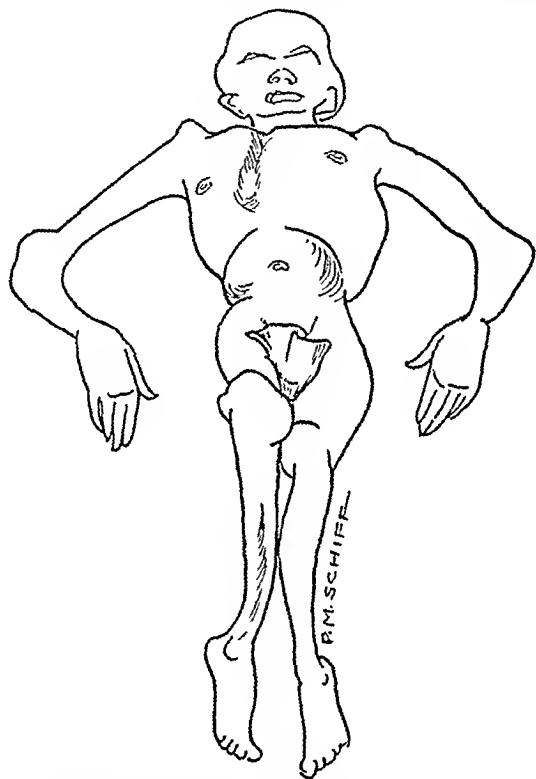


FIG. 1.—Osteogenesis imperfecta, anterior view, showing characteristic gross deformities, dwarfism and generalized muscular atrophy.

He has never been able to walk unaided. His chief means of locomotion is crawling, or walking with the aid of crutches. Because of his physical disability he was advised by his physicians to leave school after having passed the sixth grade. His appetite has always been good and there has been no diarrhea or constipation.

He has had the usual childhood diseases such as measles, mumps, scarlet fever, and chickenpox. His family history revealed that no other members were subject to such a multiplicity of fractures. However, two brothers had definite blue scleræ. Information obtained from his grandparents revealed that none of his remote relatives was known to be afflicted with this type of bone disease.

Physical examination revealed a poorly nourished, under-developed, dwarfed white male, 3½ feet in height, and weighing 44 pounds (Figs. 1 and 2).

Gross inspection of his body revealed what appeared to be generalized muscular atrophy. The head was characteristically shaped (Figs. 3 and 4). The zygomæ and mastoid processes were prominent, also the occiput, the latter increasing the antero-posterior diameter of the head. The hair was blond, and was normal in quantity and consistency. The eyebrows and eyelashes were black. These stood out in striking contrast to the color of the hair. Examination of the ears was negative. Hearing was normal to the whispered voice and tuning fork tests. The scleræ were of an intense slate-blue color. The pupils were round, equal and regular, and reacted to light and accommodation. Extraocular movements were normal. Eye ground examination was normal. The mouth was in poor condition. The mucous membrane was congested. The teeth were poorly developed, and many were carious and broken off at the gingival line. The tonsils were hypertrophied and cystic, but did not contain pus. The tongue was somewhat hypertrophied and furry. The breath was foul.

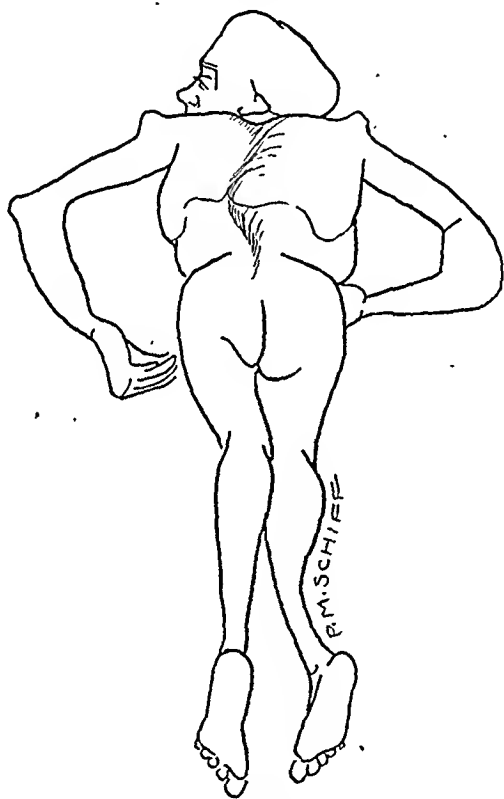


FIG. 2.—Osteogenesis imperfecta, posterior view, showing characteristic gross deformities, dwarfism and generalized muscular atrophy.

The chest (Figs. 1 and 2) was asymmetrical and deformed; the sternum prominent; the general contour that of a rachitic. The upper thoracic spine showed a scoliosis to the left. The antero-posterior diameter of the chest was increased. The ribs were not tender. No pulmonary or cardiac abnormality was noted. The abdomen was short (Fig. 1), but otherwise negative. A non-tender liver was palpated on inspiration at the right costal border. The pubic hair was sparse, the escutcheon masculine. The genitalia were normal in development. There was marked deformity of all extremities. Both upper extremities presented lateral bowing, most

pronounced in the radii and ulnæ. Both femora were abnormally short and greatly deformed. The legs presented obvious anterior bowing. The hands and feet, however, were normal. No exostoses were palpable on any of the extremities. Neurologic examination was normal throughout. Intelligence was normal.

Laboratory findings revealed negative Wassermann and Kahn tests. Repeated urine examinations failed to disclose any abnormalities. Phenol-



FIG. 3.—Osteogenesis imperfecta, showing the characteristically shaped head with bulging of the temporal regions.



FIG. 4.—Osteogenesis imperfecta, showing the characteristically shaped head with an unduly prominent occiput.

sulphonephthalein excretion, after intravenous injection, showed 80% elimination of the dye at the end of 1 hour, and 15% more at the end of the second. Repeated blood examinations revealed a red blood count of about 3,800,000; white blood count, 6300; hemoglobin (Newcomer), 10.9 gm. The differential count showed 80% neutrophils, 1% eosinophils, 15% lymphocytes, and 4% monocytes. The total plasma nitrogen was 900.6 mg.%; non-

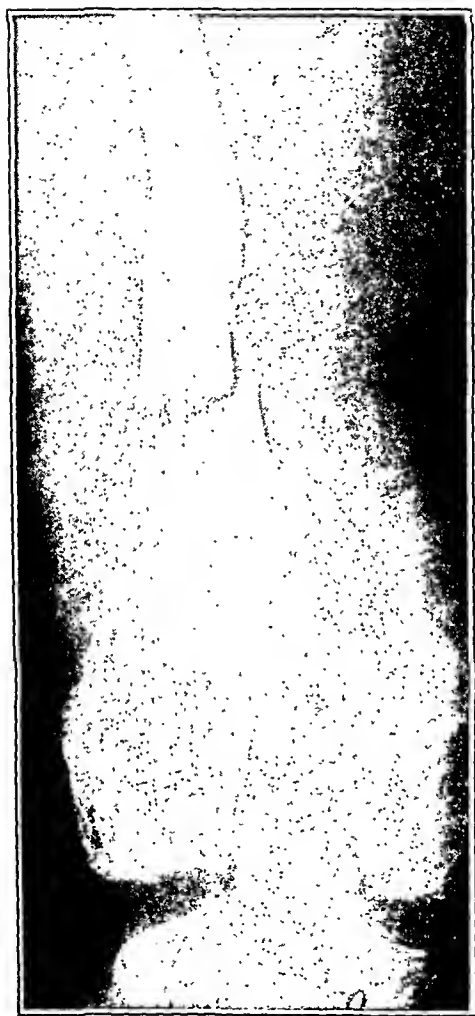


FIG. 5.—The right femur, presenting the great disproportion between the size of the epiphysis and diaphysis.



FIG. 6.—The right femur. showing the usual type and site of fracture.



FIG. 7

FIG. 7.—A fracture of the upper end of the left humerus and lateral bowing in the region of the elbow.



FIG. 8

FIG. 8.—The right femur in 1931, showing no sites of the numerous old fractures. Also showing "a foamy epiphysis," and mottling of the metaphysis. The diaphysis is particularly involved and presents a concentric type of atrophy.



FIG. 9.—Marked anterior bowing of the leg bones independent of fractures.

protein nitrogen 22.7 mg.%; blood urea was 18 mg.%; plasma protein was calculated as 5.5%. The basal metabolic rates, on two determinations, were +11 and +7, respectively.

Roentgenographic Study. A complete roentgenographic study of the skeleton of this patient was made. There were also available roentgenograms of the 15 treated fractures sustained since 1927, during a period of 7 years. These fractures had occurred with decreasing frequency. Five occurred in 1927, 3 in 1928, 3 in 1929, 1 in 1930, 2 in 1931, none in 1932, 1 in July of 1933, and none for the past 8 months. The fractures (Figs. 5, 6 and 7) during this period of 7 years, usually occurred at the ends of the diaphyses. They have been of the simple oblique or transverse type. They have never been comminuted nor compound. "Foamy epiphyses" and mottling of the metaphyses are present.

Our recent roentgenographic study of this patient shows few sites of old fractures, since psathyrotic bone heals with little callus formation. Normal bone heals with abundant callus formation. This "remarkable reparative property" of psathyrotic bone may be but another manifestation of some fundamental deficiency. The great disproportion between the size of the epiphyses and the diaphyses is another striking feature, especially of the femora (Fig. 8). The epiphyses appear to be normal, save for obvious osteoporosis. The diaphyses present a concentric type of atrophy, *i. e.*, the shaft is slender, the cortex thin, and the marrow cavity narrow. The deformities of the long bones and ribs are varied.

The skull is characteristically shaped. The calvarium is moderately thin and presents some mottling. The occiput is unduly prominent. The facial bones are small and rarefied. Many of the teeth are chipped. The pelvis is asymmetrical, and presents a mottled appearance and a high degree of osteoporosis. *The bones of the hands and feet are relatively normal.* These bones have never been fractured.

Metabolic Studies. We have investigated the total calcium balance and the iodine and chlorid balances of this patient. In our calcium studies we followed, essentially, the principles set forth by Bauer and Aub.²² Seven days prior to the calcium investigation, the patient was placed on a constant low calcium diet which he chose from Aub's table.²² The daily fluid intake was kept at about 2000 cc. The salt intake and acid base values of the diet were kept constant. This was a low iodine and chlorid-containing diet. The patient was kept on this regimen throughout the 8-day period of investigation. The patient was attended by nurses trained in the conduct of patients during mineral metabolism studies. The urine was collected in 24-hour specimens. The feces were collected in 2 periods of 4 days each.

The serum calcium was determined by the Clark-Collip method.²³ Urinary excretion of calcium and water calcium were determined by the Shohl-Pedley method.²⁴ Determination of fecal calcium was essentially by McCrudden's titrimetric method;²⁵ an aliquot part of the feces being oxidized in silica at a low temperature with the aid of oxygen. The calcium content of food was calculated from Sherman's²⁶ and Aub's²² tables. The serum phosphorus was determined by the Bell-Doisy method.²⁷ The Whitehorn method²⁸ and Harvey's modified Volhard method²⁹ were used to determine the blood chlorid and the urinary excretion of chlorid. The Phillips-Curtis method³⁰ was used to determine the blood iodine and the urinary elimination of iodine.

Results and Interpretations. Although we have presented the figures actually obtained (Table 1), the results can be more readily appreciated by an inspection of the graph (Fig. 10). These findings

TABLE 1.—CALCIUM STUDIES ON A LOW CALCIUM DIET.

Date.	Weight, kg.	Calcium.					Blood serum.	
		Urine, mg.	Feces, mg.	Output, mg.	Intake, mg.	Nega- tive balance, mg.	Cal- cium, mg. %.	Inor- ganic phos- phorus, mg. %.
10/22/33	20.4	142	168	310	175	135	9.9	3.1
10/23/33	161	168	329	175	154		
10/24/33	238	168	406	175	231		
10/25/33	19.4	134	168	302	175	127	10.5	2.5
10/26/33	139	104	243	175	68	10.2	2.7
10/27/33	161	104	265	175	90		
10/28/33	19.8	197	104	301	175	126		
10/29/33	166	104	270	175	95		
Average	20.0	167	136	303	175	128	10.2	2.7

OSTEOGENESIS IMPERFECTA

B N. ♂ 17, No. 335288.

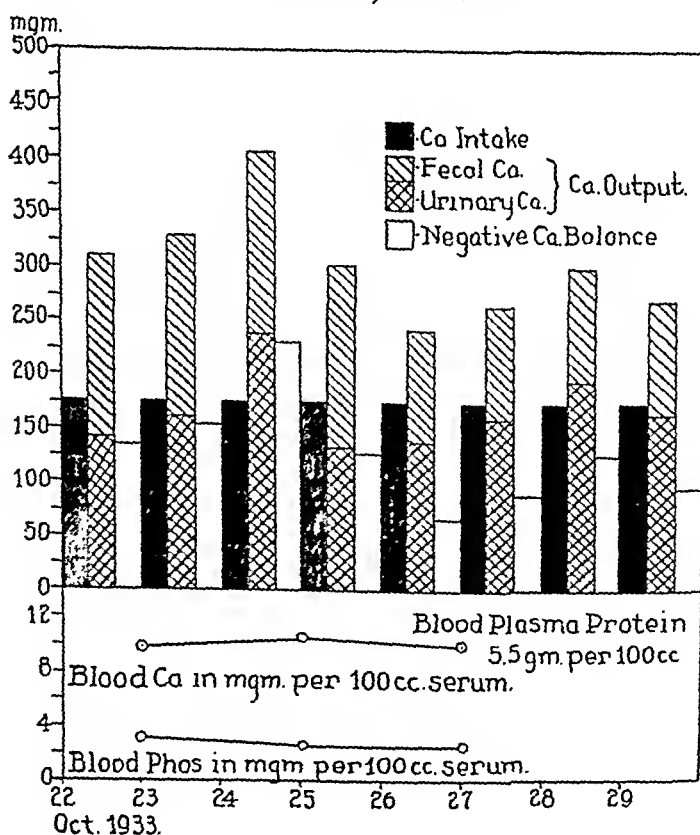


FIG. 10.—Graph of the calcium metabolism data from Table 1.

reveal no evidence of hyperparathyroidism. The serum calcium and phosphorus are normal. The urinary excretion of calcium is normal. The patient is in a continuous but normal negative calcium balance (Fig. 11).

The plasma chlorid averaged 310 mg.%, which is low normal. The daily urinary excretion of chlorid averaged 3.9 gm. This is within normal range for the low chlorid intake.

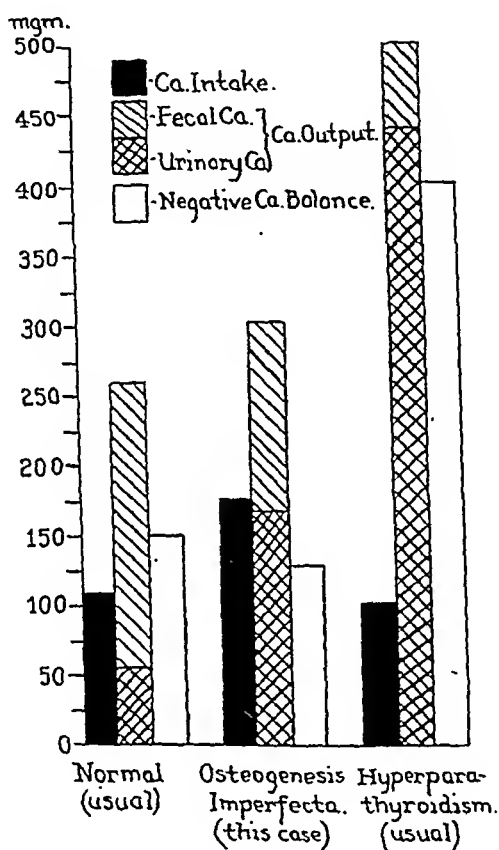


FIG. 11.—A comparison of B.N. with normal controls²² and with a case of hyperparathyroidism.³¹

The blood iodine averaged 89 micrograms%, which is greatly increased. The daily urinary elimination of iodine averaged 101 micrograms, which is increased over normal. These facts concerning the iodine metabolism are submitted without any attempt at interpretation. They indicate an increase in thyroid activity.

Summary and Conclusions. 1. Osteogenesis imperfecta occurring in a young man of 17 is reported.

2. This patient exhibited the characteristic features of: Blue sclerae, increased bone fragility, a history of 50 fractures, dwarfism,

and marked deformity. There has been a decreased tendency to fractures since puberty. No fractures of the hands or feet have occurred.

3. His brothers present the typical blue scleræ. No other members of the immediate or remote family present blue scleræ or multiple fractures.

4. The calcium metabolism of the patient revealed no evidence of hyperparathyroidism. The serum calcium and phosphorus as well as the urinary excretion of calcium and the calcium balance were normal.

5. The blood iodine was increased. The urinary excretion of iodine was increased.

6. The plasma chloride was low normal. The urinary excretion of chloride was normal.

7. Osteogenesis imperfecta does not appear to be due to hyperparathyroidism.

8. It is suggested that this disease is due to a congenital hypoplasia of the mesenchyma, perhaps associated with a deficiency in bone phosphatase production. Further study of the latter is desirable.

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SERUM PHOSPHATASE IN OSTEOGENESIS IMPERFECTA.

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A SEVERE case of osteogenesis imperfecta was recently observed at the University Hospital (service of Dr. John Gittings) from birth until death 11 weeks later, and affords the opportunity of considering the serum phosphatase increase sporadically reported in this disease. In view of the preceding article¹ in this journal, repetition of other historic, clinical and pathologic discussion of the syndrome is superfluous.

In 1923, Robison² demonstrated in ossifying animal cartilage the presence of an enzyme ("phosphatase") capable of hydrolyzing phosphoric acid esters (such as are found in normal blood^{3, 4, 16}) with the production of inorganic phosphate ions, which are readily precipitated by calcium from alkalin solution as complex inorganic salts. Its presence in cartilage which does not calcify, *e. g.*, tracheal cartilage, is not appreciable,² but its occurrence in other cartilage coincides with the appearance of the first ossification centers, as have been shown *in vivo*⁵ and *in vitro*,⁶ and its concentration varies with the rapidity of calcification, diminishing with age.⁷ Upon immersion of rachitic bone in an alkalin solution of calcium glycerophosphate or hexosemonophosphate, fresh calcium salts are deposited.⁷ For optimum activity, a temperature of 37° C., a pH of 8.4 to 9.4, and trace of magnesium in the substrate are necessary.^{4, 7, 8, 11} Under laboratory conditions, the same enzyme is allegedly capable of esterifying inorganic phosphate in the presence of suitable alcohols (glycol, glycerol and hexoses).^{9, 11}

Phosphatase is demonstrable in minute quantities in normal blood serum and corpuscles,^{4, 10, 11} and is diffused throughout the tissues, but it is relatively concentrated only in the periosteum and epiphyseal zones of bone, in intestinal mucosa, and in kidneys (after acquisition of excretory function).^{12, 13} Its concentration in serum is higher during childhood than in adult life,⁴ physiologically increasing during the absorptive period of digestion, especially with carbohydrate food, and diminishing with post-hemorrhagic anemia, malnutrition or starvation.^{14, 15} The enzyme is excreted by the kidneys at a rather constant rate, even when present in abnormal concentration in the blood.¹²

The biochemical assay of this enzyme depends upon the amount of phosphate liberated by hydrolysis of β -glycerophosphate under return to normal under adequate therapy a valuable guide in

standard conditions. Unfortunately, several modifications of the original method have created much ambiguity concerning the unit. The normal ranges for three of the best known methods are presented, but independent investigators¹⁹ find more variation in the convenience of the technique than in the accuracy of the results.

NORMAL RANGE OF SERUM PHOSPHATASE (IN ARBITRARY UNITS).

Method.	For Children.		For Adults.	
Kay ⁴	0.17 to	0.34 Aver. 0.26	0.10 to 0.21	Aver. 0.15
Jenner and Kay ³²	5.00 to 7.00	Aver. 6.00
Bodansky ^{21, 31, 33}	5.10 to 13.10	Aver. 7.30	2.00 to 3.50	Aver. 2.60

Normal blood contains phosphoric acid esters susceptible to the hydrolytic action of this enzyme,^{3, 4, 16} as well as the ionized calcium and suitable alkalinity necessary for precipitation of complex calcium phosphate. Wells' concept¹⁸ of ossification as a physico-chemical precipitation of calcium carbonate and phosphate is now supplemented by this enzymatic release of phosphate ions at the site of ossification, the enzyme apparently being formed by the hypertrophic cartilage cells found there.⁶ The selective affinity of bone for lead, radium and other similar metallic ions pathologically present is readily understood from this viewpoint. The phosphatase present in the kidneys apparently plays no part in the excretion of phosphate in the urine, which is regarded as an overflow of the inorganic phosphate present in the blood.¹⁷ The rôle played by phosphatase elsewhere in the body, and the interpretation of abnormal concentration in the serum are subjects for speculation at the present time.

Kay and Robison, of England, and Bodansky and Jaffe, of New York, have studied the serum phosphatase in a variety of clinical conditions. Kay¹² feels that the deficiency of bone formation with abnormal softening permits a slow leakage of phosphatase into the blood, perhaps by being "squeezed out" of the pliable bone, and that the uniform rate of renal excretion permits a steady rise in the blood concentration of the enzyme. Bodansky and Jaffe^{20, 21} object to this concept chiefly because of the ready physiologic fluctuation in normal individuals (*vide supra*), and believe that phosphatase variation is an expression of the capacity of bone for "cellular activities," associated with the formation of abnormal bone (Paget's disease) or osteoid tissue (rickets), and not with bone destruction *per se*.

Clinically, the concentration of serum phosphatase is found elevated (often 10 times normal) in obstructive jaundice (except in some anemic patients), and in generalized bone diseases (osteitis deformans, generalized osteitis fibrosa, osteomalacia, rickets).^{12, 22, 23} The test has a practical application in rickets,²⁴ where the increase is an accurate index of the activity of the process, and its subsequent

treatment. In the other conditions the increase is usually of more academic than clinical value in the light of present knowledge.

We have found in the literature 23 cases of osteogenesis imperfecta (fragilitas ossium) that include serum phosphatase studies, age and sex of the patient; but very rarely is there specific mention of blue scleræ, otosclerosis, and ultimate outcome of the case. Any one of such factors might show some correlation with the inconstant moderate rise in phosphatase level. In addition, Hansen²⁷ mentions 3 cases, and Fraser³⁰ "several" with "normal" serum phosphatase, but with insufficient data for our tabulation here. Excluding 1 case with active rickets,²¹ 8 of the remaining 22 patients showed a moderate elevation, ranging from 1.3 to 2.8 times normal average levels. Five of these 8 patients were in the 5- to 7-year age group, while 6 of them were female. Bearing in mind the "several" cases with normal phosphatase levels not included, an average twofold increase in serum phosphatase has been reported in less than 30% of the cases, chiefly between the ages of 5 and 7 years.

Hansen²⁷ has published the only report of phosphatase tissue distribution in this syndrome, based upon study of a 7-year-old girl, whose antemortem serum phosphatase level was "normal." He found a virtual absence of the enzyme in the periosteum and subperiosteal structures, and an extremely low concentration in the duodenum. In the blood and in other tissues no significant variation from normal values was demonstrated.

TABLE 1.—PHOSPHATASE VALUES IN OSTEOGENESIS IMPERFECTA (FRAGILITAS OSSIUM).

Reported by:	Diagnosis.	Age (yrs.).	Sex.	Serum phosphatase, Kay. Bodansky.	Degree of elevation.	Other factors.
Hunter, D. ²³	Osteog. imp.	42	M	0.162u	Normal	
Bodansky, A. ²¹	Frag. ossium	38	M	2.4u	Normal	
Dry, T. J. ²⁶	Osteog. imp.	33	F	"Normal"	Normal	
Kay, H. D. ⁴	Frag. ossium	27	M	0.16u	Normal	
Hunter, D.	Osteog. imp.	20	M	0.168u	Normal	
Hunter, D.	Osteog. imp.	17	M	0.331u	Normal	
Hunter, D.	Osteog. imp.	12	F	0.223u	Normal	
Hunter, D.	Osteog. imp.	9	M	0.27u	Normal	
Hunter, D.	Osteog. imp.	9	M	0.374u	1.4 X Normal	
Kay, H. D.	Frag. ossium	9	M	0.27u	Normal	0.33u 1 mo. later.
Kay, H. D.	Frag. ossium	7	M	0.54u	2 X Normal	
Hansen, A. E. ²⁷	Osteog. imp.	7	F	"Normal"	Normal	Autopsy studies.
Bodansky, A.	Frag. ossium	7	M	35.2u	5 X Normal	Active rickets.
Kay, H. D.	Frag. ossium	6	F	0.66u	2.5 X Normal	
Kay, H. D.	Frag. ossium	6	F	0.51u	2 X Normal	
Bodansky, A.	Frag. ossium	5	F	9.9u	1.3 X Normal	Anemia.
Bodansky, A.	Frag. ossium	5	F	19.1u	2.8 X Normal	
Bodansky, A.	Frag. ossium	3	M	7.0u	Normal	
Crooks, J. ²³	Osteog. imp.	2	F	0.30u	Normal	
Kleinberg ²⁹	Osteog. imp.	2	M	"Normal"	Normal	
Authors' case	Osteog. imp.	3 mos.	F	0.442u	1.7 X Normal	Anemia
Kleinberg, S.	Osteog. imp.	2 mos.	F	15.6u	2.2 X Normal	
Crooks, J.	Osteog. imp.	8 days	F	0.30u	Normal	

Case Report. A living female infant weighing 4 pounds and 8 ounces was born (spontaneous breech) April 17, 1935, after 5 hours' labor, the second child of a Wassermann negative 22-year-old white woman whose previous baby is normal and well, aged 20 months. In previous good health, the

mother was confined to bed 1 week during the first trimester of this pregnancy, suffering with a "nervous breakdown," and her diet throughout gestation has been apparently quite deficient owing to her aversion for vegetables and meat. Despite this her weight increased from 98 to 125 pounds. She first attended the prenatal dispensary in February, 1935, and was examined monthly thereafter without evidence of abnormality until her admission to the hospital in active labor 2 weeks prior to the expected date of confinement. No evidence of disease or deformity was discovered on physical examination, and her convalescence was entirely uneventful. Careful Roentgen studies of her entire skeletal system revealed no abnormality, and her serum calcium (10 mg. per 100 cc.) and phosphorus (4.1 mg. per 100 cc.) were within normal limits. The father has likewise enjoyed good health. An aunt and allegedly other more distant paternal relatives had blue sclerae, but neither brittle bones nor otosclerosis has been recognized among them.

The infant at birth presented the extensive deformities of the extremities that are shown in the accompanying picture. The head was large, the hair silky and rather abundant, and the ossification of the head was appreciable only in the temporal bones and in those composing the face. The cranium was likened to a "bag of skin," and the sclerae were decidedly blue. Many nodules were palpable through the thin subcutaneous tissue along the ribs, and a few subcrepitant râles were detected in the lungs. The heart sounds were of good quality, without murmurs, and no abnormalities could be demonstrated in the abdomen or genitalia. There was marked varus of the left knee and valgus of the right knee, accompanied by hyperabduction deformity of the right femur. The arms were in semi-abduction and flexion. The knee joints were partially ankylosed, and the elbows resistant to mobility. Preternatural movement was especially noteworthy in the right femur and the right humerus.

Roentgen studies revealed 14 fractures with much evidence of healing in the extremities, innumerable fractures of the ribs, and a general lack of normal radio-opacity of the bones. The urine and blood count were not abnormal, but a secondary anemia (71% hemoglobin, Sahli method) developed during the 3 months of life. The serum calcium (10.4 mg. per 100 cc.) and phosphorus (5.7 mg. per 100 cc.) were within normal limits, while the serum phosphatase determination (Dr. F. William Sunderman) of 0.442 unit (Kay) was 70% above the average normal and 30% above the upper limit of normal for infants.

The child was placed on an evaporated milk-Karo formula, but its weight never reached 5 pounds during the 11 weeks of life. Regurgitation of food and variable low fever without apparent cause were frequently encountered. The child was decidedly vegetative, lying almost motionless, and apparently unresponsive to sounds sufficient to elicit evidence of recognition in normal infants. Therapy was limited to vitamin preparations and daily sun-lamp irradiations. A temperature of 103° F. without recognizable cause occurred on the last day, but the child was unexpectedly found dead on July 7, 1935, aged 81 days.

Autopsy Findings. (No. 35-129, 14 hours after death by Dr. O. N. Smith.) The body was that of a moderately emaciated, deformed, female infant, weighing 2050 gm. The head was large, the face small, and the ears displaced somewhat caudally. The anterior calvarium was partially calcified, but flexible to palpation. The posterior aspect of the cranium was flattened and very soft. The anterior fontanelle was widely patent, and the sutures were not united, although the margins were in apposition. The hair was scant over the frontal region, but of fair growth over the parietal and temporal areas. The bitemporal circumference of the head was 33 cm., its



PLATE I.—Roentgen picture taken the day after birth, showing generalized rarefaction of bone, multiple fractures with marked callus formation, and extensive deformities.

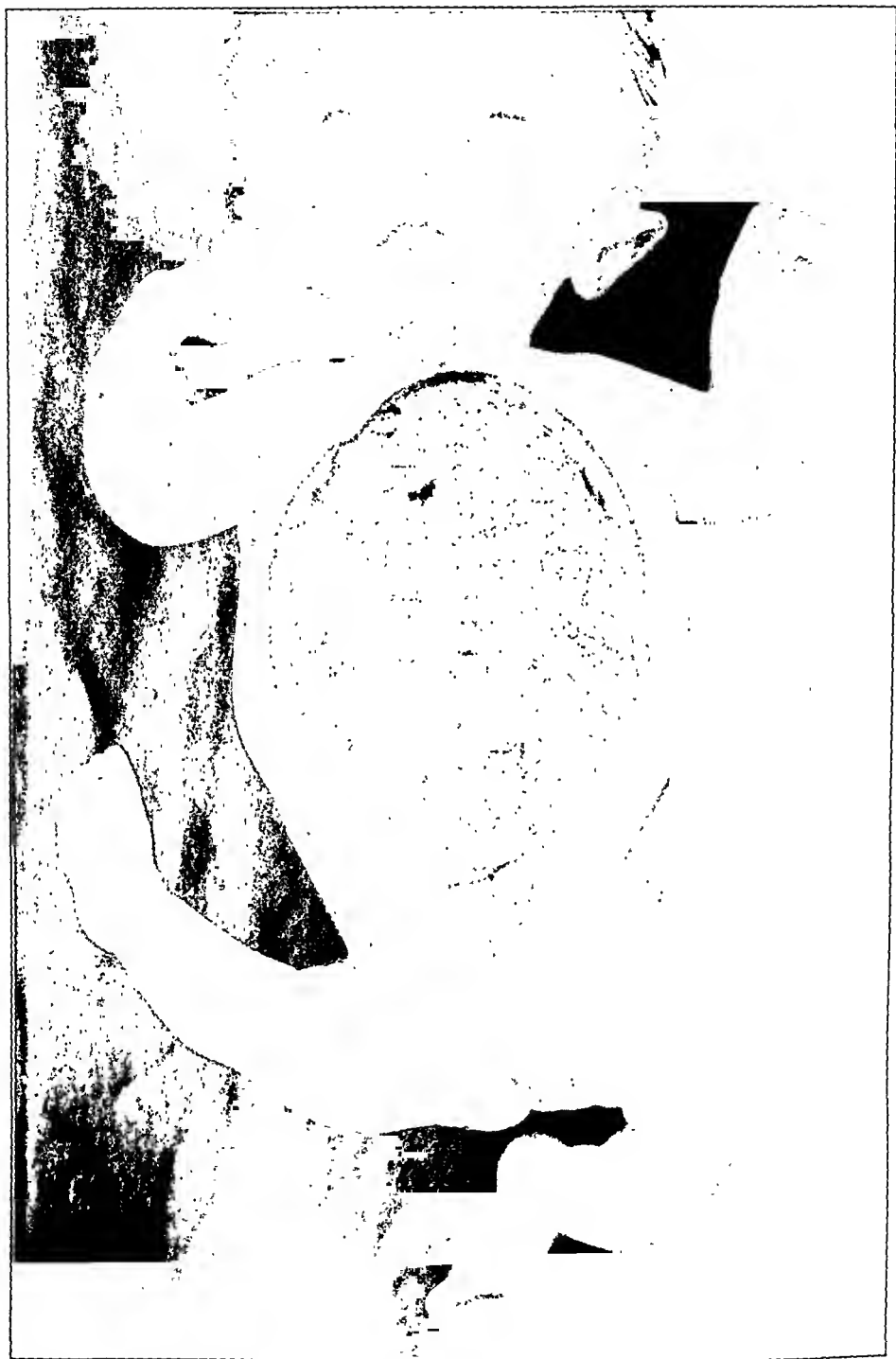


PLATE II.—Postmortem photograph of the patient, with thoracic contents removed, showing the beading of the ribs.

vertical height 12 cm., and the length of the trunk 20 cm. The deformities of the extremities were essentially the same as at birth, but preternatural mobility was no longer present.

Gross and microscopic study of the viscera (including the thyroid, parathyroid, thymus and adrenals) revealed no striking abnormality. There was microscopic passive congestion with slight edema of the lower lobe of the left lung. The ovaries were large, each measuring 10 by 6 by 4 mm.; and contained several rather large follicle cysts. No brain lesion was found, nor could pus be demonstrated in the middle ears.

Pathologically, the skeletal lesions were of paramount interest. The occipital bones consisted of a mosaic of an uncountable number of small irregular fragments, simulating shattered eggshell, and diploic marrow was visible only in the anterior portion of the cranium. The ribs were irregularly beaded with 85 distinct nodules of callus, and each clavicle showed a single healed fracture. Including the 14 fractures of the long bones of the extremities previously noted, there was present a total of 101 fractures with evident healing. The bulk of the vertebral bodies consisted of cartilage, giving little resistance to the knife.

Microscopic study of stained (hematoxylin-eosin and Mallory's connective-tissue stain) sections from the vertebrae, ribs, femur, tibia and fibula showed the diaphyseal abnormalities described as characteristic of this disease. The periosteum was considerably thickened with fibrous tissue. The cortex presented an extremely thin, discontinuous osseous shell supported by uncalcified fibrillar substance, less dense and more cellular than the periosteum. The trabeculae were diminished in number, imperfectly calcified, and sparsely scattered with little continuity; there was marked irregularity in lamellae. The osteocytes were larger and much more closely packed than in normal bone. Many osteoblasts lined the margins of the trabeculae, and were underlaid by a narrow pallid zone of uncalcified preosseous substance. Howship's lacunae were rather sparse but large, the majority containing osteoclasts. In the ribs, the fractures were the seat of annular rings of uncalcified compact hyalin cartilage, appearing on cross-section as a subperiosteal wedge with the apex directed inward. In the long bones the fracture lines were marked by fibrillary healing, with definite increase in the number of trabeculae bordering the zone of fibrous repair. The normal continuity of cancellous bone was nowhere evident, obviously as the result of numerical lack of trabeculae, but the resemblance to normal was closer in the vicinity of these fractures.

Conclusions. 1. The origin, distribution and excretion of phosphatase and its rôle in normal individuals is briefly reviewed.

2. In the cases of osteogenesis imperfecta reported with serum phosphatase studies, an increase averaging about twice normal occurs in less than 30%, chiefly in patients between the ages of 5 and 7 years. In the remaining 70% the serum phosphatase was within normal limits.

3. This elevation is of more academic interest than of clinical value at this time, as its mechanism is not yet understood.

4. A severe case of osteogenesis imperfecta is presented, with notes on the clinical course (81 days) and autopsy findings. The serum phosphatase in one determination was 1.7 times the average normal level.

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- (Titles have been omitted for sake of brevity.)

THE ELEVATED BLOOD UREA OF ACUTE GASTRO-INTESTINAL HEMORRHAGE AND ITS SIGNIFICANCE.

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THE occurrence of elevated blood nitrogen figures in acute gastro-intestinal hemorrhage has received little consideration in recent medical literature, aside from the contribution of Sanguinetti,¹ which was published since the inception of this investigation. In the present report, 42 cases of hemorrhage due to peptic ulcer are analyzed, with particular reference to the presence of azotemia and its significance. The data are summarized in Table 1.

TABLE 1.—BLOOD CHEMICAL AND ASSOCIATED FINDINGS IN 42 CASES OF HEMORRHAGE DUE TO PEPTIC ULCER.

	Sex.	Age.	Urea.	H.*	Interval, acute hemorrhage to blood analysis.	
					3d or less.	More than 3d.
Group 1: 17 cases . . .	M 14	28-68	40-103	21-96	14	3
Blood urea more than 38 mg. per 100 cc. . . .	F 3	Av. 49	Av. 58	Av. 60		
Group 2: 25 cases . . .	M 18	17-63	Less than 38	20-95	4	21
Blood urea less than 38 mg. per 100 cc.	F 7	Av. 39		Av. 53		

Blood chlorids, uric acid, creatinin and alkaline reserve were within normal limits. A moderate leukocytosis and elevated blood sugar were usual in Group 1. All cases of both groups had normal blood pressure, negative urinary albumin and sediment and urine concentration of 1020 or better. No deaths.

While the maximum normal range of blood urea is from 10 to 50 mg. per 100 cc., most analyses fall between 18 and 38 mg.,² and consequently the last figure may be taken as the usual normal upper limit. Of the 42 cases studied, 17 (42%, Group 1) had blood urea over 38 mg. per 100 cc. Of these, 10 were over 50 mg. per 100 cc. Twenty-five (58%, Group 2) had blood urea well within normal limits and served as a control group for those with elevated nitrogen figures.

Neither sex nor age can be considered to be of significance in the causation of the abnormally high figures of Group 1, although the group with elevated urea averaged 10 years older than the normal group. No significant correlation between the degree of anemia *per se* and the azotemia was noticeable. In fact, the average hemoglobin of the normal group (53%) was lower than that of the azotemic group (60%).

When consideration was given, however, to the time relation between the occurrence of the hemorrhage and the taking of the blood samples for analysis, it immediately became apparent that the high nitrogen figures were found almost exclusively in those examined within 3 days of the acute episode. Thus, 14 of the 17 patients of Group 1 had suffered their hemorrhages within 72 hours of the taking of the blood samples (11 within 24 hours). Of the group with normal nitrogen figures, only 4 had their hemorrhages within 3 days; the remainder, anywhere from 3 days to several months before. Further, as would be expected, the first group as a whole is one of acute hemorrhage, usually with vomiting of considerable amounts of blood, and requiring immediate hospitali-

* H = Hemoglobin, Sahli.

zation. The second group is made up for the most part of chronic bleeders, although some had had a severe acute hemorrhage a long time before the taking of the chemistry.

The elevation of urea nitrogen in acute gastro-intestinal hemorrhage probably depends on several factors. Sudden blood loss in itself will cause an increase in the blood non-protein nitrogen figures,^{3,4} as will shock.^{5,6} These, of course, play a part in cases of gastro-intestinal hemorrhage, causing accelerated protein catabolism. Dehydration, too, will tend to raise blood nitrogen.⁷ This factor was probably not negligible in the present series. Although gastric hemorrhage cases admitted to this hospital are routinely put on the diet recommended by Andresen,⁸ in which an adequate amount of fluid in the form of gelatin solution is given, nevertheless the dehydration would hardly have been righted in the short interval before the taking of a blood sample. In this diet there is a significant amount of protein, but since the entire series was treated similarly, this cannot be considered a factor. The brief enforced starvation during the period of blood loss and dehydration may play a part,⁹ although probably not as much with the Andresen as with other forms of treatment.

Impairment of kidney function probably was not concerned, as evidenced by normal blood pressure, good urine concentration and negative urinary albumin and sediment. Experimentally, kidney excretion of water is unimpaired by extensive bleeding.¹⁰ Sanguinetti, too, does not consider that kidney dysfunction plays any part in the azotemia of gastro-intestinal hemorrhage.¹ With him we may feel that the most significant factor implicated is the appreciable quantity of nitrogen represented by the protein of the blood liberated into the gastro-intestinal tract. The absorption of this would cause a considerable elevation of the blood figures, particularly in cases where bleeding is continuous, although vomiting is not marked, and constipation is present as a result of morphin and the recumbent posture.

The azotemia of acute gastro-intestinal hemorrhage probably in itself plays little part in the clinical symptomatology, since it rarely reaches uremic proportions in cases uncomplicated by other adequate causes of elevated blood non-protein nitrogen figures. In this series, which is composed of uncomplicated cases, there were no deaths. In 1 case of cirrhosis and diabetes mellitus with very severe gastro-intestinal hemorrhage, due to a ruptured esophageal varix, there was definite uremia on admission, with a blood urea of 160. At autopsy this man had severe degenerative parenchymatous change of the kidneys. In uncomplicated cases, however, a urea above 102.7 was never noted, and uremia never played an appreciable part in the clinical picture. One can hardly, therefore, regard the azotemia with as much apprehension as Sanguinetti,

and certainly it does not seem that one would ever be driven to so drastic a procedure as cecostomy to insure the elimination of retained blood, as he suggests, should surgical intervention be indicated.

That determinations of the blood urea may have definite prognostic significance cannot be denied, as Duval and Grigant demonstrated in the instance of shock due to wounds⁶ and as Sanguinetti and I have also observed in gastric hemorrhage. Thus, in the complicated case cited above, with persisting hemorrhage the urea rose to 246 before death. Similarly, in a fatal uncomplicated case, seen since the compilation of the data in this paper, the persistence of azotemia 1 week after the original chemical determination indicated continuing hemorrhage and presaged the patient's death. The fact that the elevated urea was not usually observed in cases seen more than 3 days after the acute hemorrhage agrees with Sanguinetti's observation that the maximum figures are attained on the third or fourth day. There is a rapid return to normal with cessation of hemorrhage. This was so in 2 cases reexamined on the eighth and ninth days. It is probable, therefore, that a closer watch of the chemical composition of the blood in patients with gastro-intestinal hemorrhage who do not do well clinically may confirm the impression of persisting hemorrhage and may indicate the necessity for more radical, possibly surgical, treatment.

Dr. A. F. R. Andresen has brought to my attention Christianson's very recent report of 21 fatal cases of massive hemorrhage in peptic ulcer.¹¹ The general exhaustion which precedes death is considered to be on the basis of extrarenal hyperazotemia, preceded and accompanied by achloruria, rather than due to true anemia from persisting blood loss. This conception of the significance of uremia in gastro-intestinal hemorrhage is at variance with the impression gained from the uncomplicated, non-fatal cases reported here.

The urinary chlorids were not studied in any of the present series. Only 5 blood chlorid estimations were made (2 in Group 1; 3 in Group 2). These were normal. Nor was there any consistent abnormality in several alkalin reserve determinations made.

Of 4 fatal cases of gastro-intestinal hemorrhage, only 1, cited above, was uncomplicated. His urea did not go above 72 mg. per 100 cc. shortly before death from continuing hemorrhage. This could hardly have played any part in his death, although its persistence at this level in comparison with a previous chemistry was of prognostic significance.

Another, also mentioned above, had diabetes mellitus and hepatic cirrhosis with a ruptured esophageal varix. This patient continued to have terrific hematemesis and, although his urea climbed from 160 to 246, his blood loss was reasonably the major cause of death. Prior to death, he failed to concentrate above 1018 on 3 urine

examinations and an abnormal urinary sediment indicated the severe renal damage revealed at postmortem.

A patient with cirrhosis and ruptured esophageal varix continued to vomit blood until death. He failed to show even the usual azotemia of acute gastro-intestinal hemorrhage.

Another patient having duodenal ulcer with mild hematemesis showed a slight elevation of the blood urea at a time when the clinical picture was complicated by bronchopneumonia and jaundice.

These observations do not suggest that uremia plays any great part in the clinical picture of acute gastro-intestinal hemorrhage. The elevated blood nitrogen figures, *per se*, probably have no significant effect on the final outcome, except that, as already noted, persistent elevation may point to persistent hemorrhage.

Summary and Conclusions. 1. In cases of acute gastro-intestinal hemorrhage studied within 3 days of the occurrence of the hemorrhage, there is an elevation of the blood urea above normal. This is probably due to the nitrogen intake represented by the protein of the blood retained in the gastro-intestinal tract, plus the factors of hemorrhage, *per se*, shock, dehydration and starvation.

2. In uncomplicated cases this azotemia does not reach uremic proportions and plays little, if any, part in the symptomatology.

3. In cases with continuing hemorrhage the elevated urea persists or increases and points to an unfavorable outcome. The use of this diagnostic aid in cases which are not doing well may point to the necessity for radical intervention.

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EFFECT OF ANTICOAGULANTS ON SEDIMENTATION RATE.

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VARIOUS anticoagulants in widely different amounts have been used in determining the sedimentation rate of red blood corpuscles (Table 1).

TABLE 1.—VARIOUS ANTICOAGULANTS USED IN SEDIMENTATION TESTS.

Investigator.	Anticoagulant.	Amount.
Westergren ¹ . . .	3.7% sodium citrate	0.2 cc. to 0.8 cc. blood.
Linzenmeier ² . . .	5.0% sodium citrate	0.2 cc. to 0.8 cc. blood.
Hunt ³	1.6% sodium citrate	0.5 cc. to 3.5 cc. blood.
Cutler ⁴	3.9% sodium citrate	0.5 cc. to 4.5 cc. blood.
Jacobs ⁵	5.0% sodium citrate	0.4 cc. to 1.6 cc. blood.
Plass and Rourke ⁶ . .	Heparin	1.5 mg. dry to 5 cc. blood.
Rubin and Smith ⁷ . .	Hirudin	1.0 mg. dry to 5 cc. blood.
Cooper ⁸	20% potassium oxalate	3 drops, allowed to dry, to 15 or 20 cc. blood.
Linton ⁹	Powdered sodium oxalate	14 mg. to 5 cc. blood.
Mathieu ¹⁰	Powdered potassium oxalate	2 mg. to 1 cc. blood.

Johnson¹¹ found that dry potassium oxalate and dry heparin increased the rate of sedimentation; sodium citrate in concentrations ranging from 2.5 to 5% gave slight variations in the sedimentation rate. He failed to state the amounts of the first 2 anticoagulants used.

Walton¹² used 1 cc. of 3.8% sodium citrate to 9 cc. of blood. He states that many parallel experiments were made using various anticoagulants, such as potassium oxalate crystals, hirudin and heparin, but he gives no results, nor does he state the amounts used.

This study was undertaken to determine the effects of various anticoagulants in equimolecular and other concentrations, and the effects of using the anticoagulant dry, or with varying amounts of solvent, on more than one method. The Cutler (large and small tube), the Westergren and the Linzenmeier methods have been used. The anticoagulants used include sodium citrate, ammonium citrate, sodium oxalate, potassium oxalate, ammonium oxalate and heparin.

Since sodium citrate is used in the 3 above methods, it serves as the control. The formula is $2\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 11\text{H}_2\text{O}$, and molecular weight is 714.3. Cutler used 3%, or 0.0042 gm. mol. per 100 cc.; this is 15 mg. to 5 cc. final volume, for the large tube (0.5 cc. solvent and 4.5 cc. blood), and 3 mg. to 1 cc. for the small tube (0.1 cc. solvent and 0.9 cc. blood). Westergren uses 3.7%, or 0.0051 gm. mol. per 100 cc.; this is 3.7 mg. to 1 cc. final volume (0.2 cc. solvent and 0.8 cc. blood). If 2.5 cc. is desired as the final volume, 18.5 mg. of citrate are used. Linzenmeier uses 5%, or 0.007 gm. mol. per 100 cc.; this is 10 mg. to 1 cc. final volume (0.2 cc. solvent and 0.8 cc. blood).

Table 2 shows the amounts of the various anticoagulants, which are equimolecular to the sodium citrate used in each method:

TABLE 2.—AMOUNTS OF ANTICOAGULANTS USED IN EACH METHOD.

Anticoagulant.	Mol. wt.	Cutler.	Westergren.	Linzenmeier.
Ammonium citrate, $(\text{NH}_4)_3\text{C}_6\text{H}_5\text{O}_7$	243.2	1.0214% 5.107 mg. to 5 cc.	1.2403% 6.202 mg. to 2.5 cc.	1.7024% 3.405 mg. to 1 cc.
Sodium oxalate, $\text{Na}_2\text{C}_2\text{O}_4$	134.0	0.5628% 2.814 mg. to 5 cc.	0.6834% 3.417 mg. to 2.5 cc.	0.938% 1.876 mg. to 1 cc.
Potassium oxalate, $\text{K}_2\text{C}_2\text{O}_4 \cdot \text{H}_2\text{O}$	184.2	0.7736% 3.868 mg. to 5 cc.	0.9394% 4.697 mg. to 2.5 cc.	1.2894% 2.579 mg. to 1 cc.
Ammonium oxalate $(\text{NH}_4)_2\text{C}_2\text{O}_4 \cdot \text{H}_2\text{O}$	142.1	0.5968% 2.984 mg. to 5 cc.	0.7247% 3.623 mg. to 2.5 cc.	0.9947% 1.989 mg. to 1 cc.
Heparin in 0.9% NaCl	...	1 mg. to 5 cc.	0.5 mg. to 2.5 cc.	0.1 mg. to 1 cc.

Human blood was used throughout. In the control by each method, the determination was made as described by each author. In the studies in which the amount of solvent was varied, the anticoagulant was used, dry, with half the control amount of solvent, and with twice the control amount of solvent. The amount of blood varied accordingly, in order to keep the final volume the same as in the control.

Only the Cutler (large tube) and the Westergren results will be reported in detail. Only the 1-hour readings will be given. Table 3 presents the results. The control serves as the minuend in each case, to arrive at the difference.

In the Cutler method, increase of solvent delays and decrease of solvent hastens the rate of sedimentation. Increasing the amount of anticoagulant (sodium citrate) tends to delay the rate. Ammonium citrate gives a slight increase in the rate; sodium oxalate has little effect unless used dry. Potassium oxalate has slight effect; ammonium oxalate hastens the rate. Heparin increases the speed of sedimentation unless the amount of solvent is greater than the control amount.

In the Westergren method, as with the Cutler, an increase of

TABLE 3.—SEDIMENTATION RATES WITH DIFFERENT ANTICOAGULANTS BY THE CUTLER AND WESTERGREN METHODS.

Anticoagulant.		Cutler method (large tube).				Anticoagulant.		Westergren method.			
Mg.	Ce. solvent.	No. of cases.	Control. (Mm.)	Experi-mental. (Mm.)	Difference. (Mm.)	Mg.	Ce. solvent.	No. of cases.	Control. (Mm.)	Experi-mental. (Mm.)	Difference. (Mm.)
Sodium citrate.	0	14	4.8	5.8	-1.0	Sodium citrate.	0	30	6.5	9.4	-2.9
15.0	0.25 H ₂ O	5	4.8	5.1	-0.3	18.5	0.25 H ₂ O	10	7.0	9.3	-2.3
15.0	1.0	5	4.9	3.8	+1.1	18.5	0.75	4	6.5	5.4	+0.9
37	0.5	24	5.3	4.7	+0.6	7.5	0.25	12	6.9	9.4	-2.5
50	0.5	23	4.9	4.3	+0.6	25.0	0.5	22	5.3	5.5	-0.2
						37.0	1.0	5	4.4	2.1	+2.3
						47.5	0.5	20	8.7	5.9	+2.8
Ammonium citrate.	0.5	17	6.3	7.2	-0.9	Ammonium citrate.	0.5	38	4.1	3.5	+0.6
5.107	(equimolecular, 1.0214%)					6.2016					
7.5 (1.5%)	0.5	50	10.2	13.6	-3.4	(1.2403%)					
Sodium oxalate.	0.5	106	6.9	7.0	-0.1	Sodium oxalate.	0.5	36	3.5	2.9	+0.6
2.814	(equimolecular, 0.5628%)					3.417					
8.0	0	8	5.7	7.1	-1.4	(0.6834%)	0	5	1.7	2.6	-0.9
8.0	0.5	10	7.0	7.0	0	0.64	0.5	5	1.7	1.8	-0.1
8.0	1.0	5	3.2	2.8	+0.4	0.64					
Potassium oxalate.	0.5	34	6.8	7.4	-0.6	Potassium oxalate.	0.5	50	7.4	7.4	0
3.868	(equimolecular, 0.7736%)					4.6971					
8.0	0	4	4.9	5.4	-0.5	(0.9349%)	0	5	2.3	3.0	-0.7
8.0	0.5	5	5.0	4.7	+0.3	8.0	0.5	5	2.3	2.3	0
Ammonium oxalate.	0.5	35	11.2	13.5	-2.3	Ammonium oxalate.	0.5	36	7.6	8.2	-0.6
2.984	(equimolecular, 0.5968%)					3.623					
17.5	0	5	5.9	9.7	-3.8	(0.7247%)	0.5	5	7.6	7.5	+0.1
17.5	0.5	5	5.9	8.9	-3.0	15.0					
Heparin.	0	20	5.3	7.7	-2.4	Heparin.	0	13	6.4	8.2	-1.8
1.0	0.5 NaCl	20	5.3	6.0	-0.7	0.5	0.5 NaCl	59	4.5	5.1	-0.6
1.0	(0.9%)					0.5	(0.9%)				
1.0	1.0 NaCl	20	5.3	5.4	-0.1	0.5	1.0 NaCl	19	6.1	4.3	+1.8
	(0.9%)						(0.9%)				

solvent delays and a decrease hastens the rate of sedimentation, and an increase in the amount of anticoagulant tends to delay the rate. With ammonium citrate the rate is slightly decreased, contrary to the results with the Cutler method. Sodium oxalate gives a slight retardation; potassium oxalate has little effect; ammonium oxalate gives a slight increase in rate. Heparin increases the speed of sedimentation unless the amount of solvent is greater than in the control.

The results with the small Cutler tube were essentially the same as with the large Cutler tube. In the Linzenmeier method the results of varying the amount of sodium citrate and of varying the amount of the solvent were essentially the same as with the Cutler method. Ammonium oxalate and heparin hastened the sedimentation rate; the other anticoagulants were not tried.

Summary. Although the changes in the sedimentation rate are probably not great enough to affect the clinical results markedly, the following observations are interesting. Decrease in the amount of solvent hastens sedimentation; one can expect a faster rate when the anticoagulant is used dry. An increase in the amount of solvent beyond the control amount retards sedimentation, although the blood is diluted. An increase in the amount of anticoagulant, without change in the amount of solvent, tends to retard sedimentation. Ammonium citrate increases the rate in the Cutler and decreases it in the Westergren. Sodium oxalate, potassium oxalate and ammonium oxalate tend to increase the rate in the Cutler method, in the above order. The first decreased the rate in the Westergren, the second had no effect and the third increased the rate. Heparin increases the rate in all cases, unless used with a greater amount of the solvent than the control.

Conclusions. Sodium citrate is a highly satisfactory anticoagulant for use in the sedimentation test.

Fifteen milligrams in 0.5 cc. of distilled water, or 0.5 cc. of 3 per cent sodium citrate, is sufficient to prevent coagulation in 4.5 cc. of blood; this amount does not hemolyze the red blood corpuscles. A change either in the amount of anticoagulant or in the amount of solvent alters the rate of sedimentation.

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TIGER-SNAKE VENOM IN THE TREATMENT OF ACCESSIBLE HEMORRHAGE.

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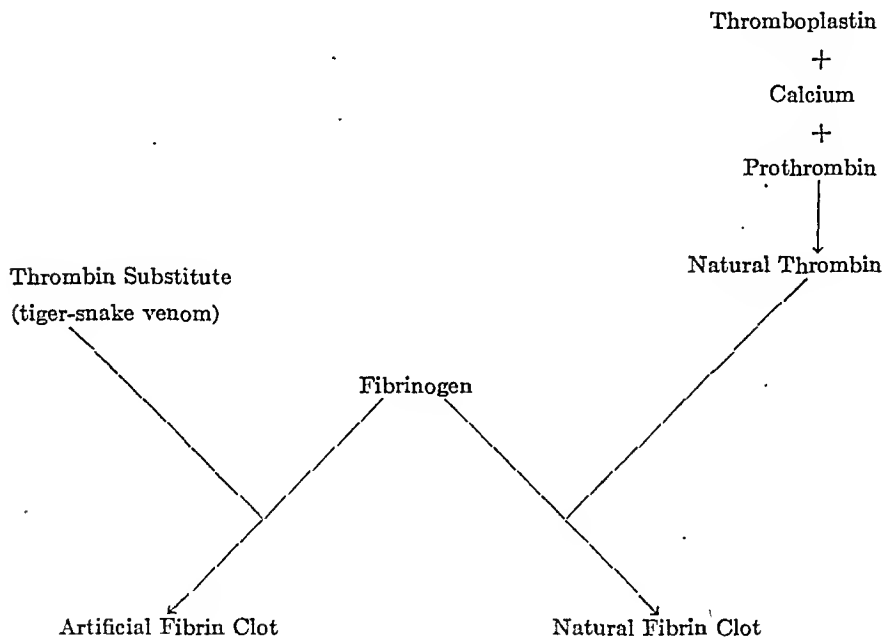
THE dry venom of the Australian tiger-snake readily clots 12,800,000 times its weight of heavily citrated or oxalated blood. Whether this fantastic clotting power may be of clinical value in the treatment of hemorrhage has been the subject of the investigations which are presented herein.

It seemed to the authors that tiger-snake venom would be superior to other local hemostatic agents for the following reasons. First, it quickly produces a firm fibrin clot; second, it hastens the clot retraction; third, it does not require preliminary collaborating factors—thromboplastin, calcium, prothrombin—to coagulate the fibrinogen. The venom acting as a thrombin substitute requires only the presence of fibrinogen to form a clot (Fig. 1.)

Knowledge of this unusual power of tiger-snake venom is based upon experiments performed by many investigators during the past 42 years. Martin¹ in 1893 first demonstrated the activity of certain Australian snake venoms—*Notechis scutatus*, the tiger snake, and *Pseudechis porphyriacus*, the black snake—in causing the coagulation of blood *in vivo*. He showed that intravascular

clotting occurred quickly when a sufficiently large dose* was rapidly injected into the blood stream. However, when the dose was smaller, the blood after a brief period (a few minutes) of increased coagulability—the positive phase—partially or entirely lost its capacity to clot for many hours—the negative phase. When such blood in the negative phase was analyzed an absence of fibrinogen was noted; and the blood did not clot even if thrombin or coagulant venom in any quantity were added^{2,3}. The blood did clot, however, when fibrinogen was added.²

FIGURE 1.



In 1905 Martin⁴ working with tiger-snake venom confirmed the findings of Lamb⁵ who had used the coagulant venom of another snake—the Russell viper of India. Martin found that minute doses of venom could coagulate *in vitro* blood which had lost the capacity for spontaneous coagulation on account of the addition of citrate, oxalate, or fluorid. He concluded that the coagulant venoms contained true fibrin ferments (thrombins). More recently Kellaway⁶ made extensive investigations in the titration and pharmacologic action of various Australian venoms, stressing the very powerful coagulant action of the tiger-snake venom. In August, 1934, the writers, in a personal communication to Dr. Kellaway suggesting its use as a coagulating agent in hemorrhagic conditions, especially in hemophilia, procured from him a supply of tiger-snake venom with which to pursue clinical studies. In November, 1934, McFarlane and Barnett⁷ using the coagulant venom derived

* 0.1 mg. (or more) intravenously for dogs, cats or rabbits.

from the Russell viper as a local hemostat, reported encouraging results in bleeding cases, including hemophilia; however no details of the treated cases were described. In 1935 Rosenfeld and Wiener⁸ described a new method of determining quantitatively plasma fibrin, basing it on the coagulant activity of tiger-snake venom.

In Table 1 the snake venoms noted for their powerful coagulant action are listed, in order of their potency. Martin⁴ regards tiger-snake venom as the most powerful, followed by the black snake, *Echis carinatus*, and *daboia*. Houssay and Sordelli³ believe the Australian venoms to be the most active, followed by the *Lachesis* group, and after these the *Vipera russellii*. The exquisite coagulant activity of tiger-snake venom is also shown by the experiments of Kellaway.^{6b}

TABLE 1.—SNAKE VENOMS HAVING A COAGULANT ACTION.

Family.	Genus and species.	Common name.	Habitat.
Colubridæ	<i>Notechis scutatus</i>	Tiger snake	Australia.
Colubridæ	<i>Pseudechis porphyriacus</i>	Black snake	Australia
Viperidæ	<i>Echis carinatus</i>	Phoorsa	India.
Viperidæ	<i>Lachesis neuwiedii</i>	Urutu	Brazil.
Viperidæ	<i>Lachesis lanceolatus</i> , or <i>Bothrops atrox</i>	Fer-de-lance	Tropical America.
Viperidæ	<i>Vipera russellii</i>	Daboia	India.

The venom of the tiger snake has been chosen for investigations for the following reasons:

1. Its clotting power is unexcelled.
2. Hemorrhagins (endotheliolysins) which produce local hemorrhagic extravasations are minimal in tiger-snake venom, whereas they are abundantly present in the Viperidæ, such as the *daboia* and the fer-de-lance (Kellaway;^{6a} Calmette⁹). Calmette states that the venoms of the Viperidæ have a much greater local effect on mucous membranes than those of the Colubridæ, and may cause a severe acute inflammation with hemorrhages. When ingested orally large amounts of the venoms of the Colubridæ are innocuous, whereas those of the Viperidæ, especially the *Lachesis* group, provoke a violent gastritis, from which the animal may die.

3. Tiger-snake venom does not appear to render tissues unduly susceptible to bacterial invasion, as do venoms of the Viperidæ (Kellaway^{6a}).

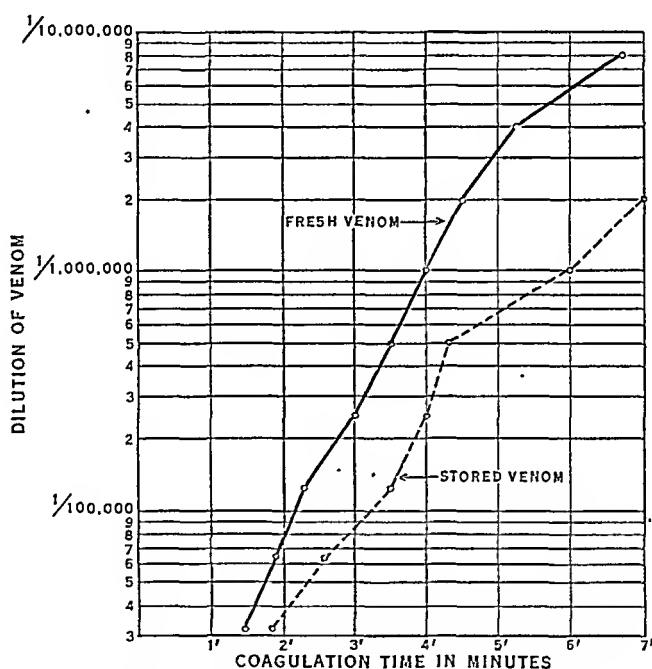
4. It has very little or no proteolytic action. On the other hand, Calmette⁹ states that the coagulant venoms of the Viperidæ produce an intense proteolysis, even in weak solutions, so that the compact clots formed at first soon become soft and may then dissolve.

While it is true that the undesirable neurotoxin is more powerful in tiger-snake venom than in Viperidæ venoms, the minimal amounts of venom required and its action in closing the channels of absorption by local thrombosis, provide for tiger-snake venom a therapeutic index well within the limits of safety.

Preliminary Experiments. Preceding the clinical work, experiments were performed to assay the properties of the venom *in vitro* and *in vivo*.

A. *Titration of the Coagulant Power of the Venom.* A rack of tubes was prepared, each containing 0.1 cc. of progressive dilutions of venom in saline, each tube having $\frac{1}{2}$ the strength of the preceding one. The resultant titers extended from 1/1000 to 1/12,000,000. A control tube containing 0.1 cc. of normal saline was also used. To each tube was added 0.4 cc. of freshly drawn whole blood, rendering the final dilutions of venom 5 times as high as the original dilutions noted above. The coagulation time was measured with a stopwatch. Although the control blood required 8 minutes to clot, the venom caused firm clot formation within 1 minute up to a dilution of 1/320,000.

Using citrated or oxalated whole blood in a similar fashion, it was found that a final dilution of 1/160,000 venom produced a clot in 1 minute. It then became apparent that if plasma instead of whole blood were used, a nicer end point could be observed, the solution acquiring a whitish opacity



GRAPH I.—(Semilogarithmic), showing the reduction in clotting power of stored venom as against fresh venom.

just before clotting took place, thereby obviating the necessity of too frequent agitation. In all subsequent titrations, therefore, citrated plasma was used. Since the coagulation time of plasma was found to increase with its age, only fresh plasma was employed. All experiments were performed at room temperature.

Graph I represents the results of such a titration with freshly prepared venom, the ordinate representing dilutions of venom, the abscissa showing the coagulation time. The superimposed dotted line represents a titration of similar venom which had been stored for 2 months in the ice box at a dilution of 1/5000 in normal saline solution. The increased coagulation time shows that the clotting power of the stored venom has been moderately reduced by allowing it to remain in normal salt solution for 2 months.

B. *The Clotting Unit.* In an effort to standardize various batches of venom and to detect deterioration in stored solutions an arbitrary clotting

unit was devised. One clotting unit was defined as the clotting power present in the highest dilution of venom which will produce coagulation of freshly citrated plasma within 2 minutes,* the plasma being added to the various tubes of diluted venom in the proportion of 4 to 1 as described above. If the titration is so performed on an unknown solution of venom and if n represents the number of the last tube in which clotting occurs within 2 minutes, then a simple formula for the calculation of the units per cc. of unknown solution = $5 \times 2^{n-1}$. Tested in this way 1/5000 solutions of our various batches of tiger-snake venom proved to contain at least 7 units per cc.

C. *The Clotting Action on Pathologic Blood in Vitro.* Blood specimens were obtained and coagulation time by the Lee and White method were determined in the following cases.

TABLE 2.—CHANGES IN CLOTTING TIMES UPON ADDITION OF TIGER-SNAKE VENOM.

Hosp. No.	Disease.	Clotting time.	
		Without venom (minutes).	With venom (seconds).
H. G. 154505	Hemophilia	(a) 5 (b) 12	(a) 50 (b) 50
B. L. 178536	Hemophilia	63	55
R. S. 178702	Essential purpura hemorrhagica (bleeding time more than $\frac{1}{2}$ hr. Platelets = 2000)	7	50
O. S. 169638	Essential purpura hemorrhagica (bleeding time = $5\frac{1}{2}$ mins. Platelets = 80,000)	$4\frac{1}{2}$	60
H. N. 178960	Acute myeloblastic leukemia (bleeding time = 20 mins. No platelets in smears)	10	45

These experiments demonstrated that *in vitro* the tiger-snake venom was efficacious in clotting the blood of patients suffering from active hemorrhagic disease. Most interesting was the observation that hemophilic blood could be clotted as easily as normal blood.

D. *Animal Experiments.* The results of animal inoculation of the venom confirmed the observations of previous authors.

1. *Coagulant Action.* A series of experiments on cats showed that 0.5 mg. per kilo given intravenously produced death within 2 minutes. Autopsy revealed extensive intramuscular thrombosis. Intravenous injection of 0.1 mg. per kilo in cats caused death in 2 hours. Before this injection the clotting time of the cat's blood was 4 minutes; 15 minutes after the injection of venom another specimen of blood was withdrawn, which showed no tendency to clot after several days' observation. Even the addition of a large amount of venom failed to produce clotting. Autopsy of such "negative-phase" animals revealed fluid blood throughout the vascular tree except for a stringy thrombus in the portal vein.

2. *Hemorrhagin.* While intraperitoneal injection into mice of 1 cc. of 1/5000 solution (0.2 mg.) of moccasin venom produced a copious sero-sanguinous peritoneal exudate, no gross sign of peritoneal irritation was noted in the mice receiving an equal dose of tiger-snake venom.

3. *Neurotoxin.* Subcutaneous injection of 0.05 mg. per kilo. regularly killed rabbits within 24 hours, whereas intravenous injection of 0.005 mg.

* Coagulation within a period of 2 minutes was selected because: 1, It is the nearest approach to clinical requirements; 2, several tubes seem to clot almost simultaneously at about this time; 3, the more delayed clots are of poorer consistency.

per kilo regularly killed them within 15 minutes. A rapid method of estimating the neurotoxic potency of tiger-snake venom was that of subcutaneous inoculation of mice. Subcutaneous injection of 0.2 mg. regularly killed mice (weighing about 15 gm.) within 30 minutes, paralysis ascending from the hind-legs to the fore-legs, the heart continuing its pulsation for several minutes after respiration had ceased.

Preparation of Venom Solutions. The dried venom was pulverized, and 100 mg. lots were weighed out on a quantitative balance. Sterile normal saline solution was added to produce the required dilution, 1/100 volume of 1% merthiolate solution being included. The resultant saline solutions of venom (1/1000 and 1/5000 containing 1/10,000 merthiolate) were stored in the ice box for 2 days and then tested for sterility. Aërobic cultures on blood plates and glucose broth were made. Since anaërobic spore-bearing pathogens have been described in snake venom (Kellaway and Williams,¹⁰) each solution of venom was cultured anaërobically and also was injected in sublethal dosage (0.1 cc. of 1/5000 solution) into the hamstring muscles of a guinea pig. No contaminant was found after the routine treatment with merthiolate. Since sterilization by ultrafiltration or heat seriously impaired the clotting power of the venom, they were not employed.

The Clinical Use of Tiger-snake Venom in Hemorrhagic Diseases. The true evaluation of a hemostatic agent is hazardous. The study of a few carefully controlled cases is more valuable than any attempt to draw a mathematical deduction from numerous poorly controlled cases. The danger that spontaneous cessation of hemorrhage may be attributed to the therapeutic agent, or that the venom packing receive credit for hemostasis which plain packing alone could achieve, is especially to be controlled and avoided. Our conclusions will therefore be valued in direct relation to: 1, The length of time that hemorrhage had persisted unabated before venom is used; 2, the failure of simple packing to produce hemostasis; 3, the promptness of the response to venom.

Since normal patients did not bleed obstinately enough to satisfy the first two requirements, the investigations were limited to cases of severe hemorrhagic disease. Even these might have given specious results if the strict controls employed had not been diligently checked. Several patients with hemorrhagic diseases, not included in the appended reports, one a true hemophiliac with a coagulation time beyond 1 hour, stopped bleeding while the control treatments were being applied, before venom was used. As a general rule, venom was not used unless no diminution of the hemorrhage had been observed after sufficient trial of other common hemostatic agents.

Case Reports. CASE 1.—*Thrombocytopenic Purpura Secondary to Arsenic Poisoning.* S. G. (Hosp. No. 154505), male, aged 51, a furrier, with occupational exposure to arsenic dyes, was first admitted 3 years previously for pallor, tarry stools, and purpura of the skin. Anemia, thrombocytopenia, increased bleeding time, delayed clot retraction, and discovery of arsenic in the urine confirmed the diagnosis. During the following 6 months two episodes of severe hemorrhage after dental extraction occurred. During the past 2 years he has had sporadic hemorrhagic exacerbations, the gums

often bleeding for several days continuously. Pressure with plain gauze and with thromboplastin packings did not control the hemorrhage, blood oozing through the gauze for hours and even days until cessation occurred spontaneously or after transfusion. During an exceptionally severe exacerbation when the patient had bled continuously for 3 days from the gums with no decrease in the flow, tiger-snake venom was used. The blood findings at the time were similar to those described above. Systemic application of plain absorbent cotton and gauze packings, each held for at least 5 minutes against the bleeding area in the left lower gum, failed to check the flow. Systematic application of thromboplastin dressings were also futile, the blood oozing through the dressings. Finally after 1 hour of these control experiments, absorbent cotton wrung out in 1/5000 tiger-snake venom was pressed against the bleeding area. In 2 minutes bleeding had ceased. After an hour the venom pledget was removed, and copious bleeding recurred. Again thromboplastin and gauze packings failed to stop the flow and once more a venom pledget produced hemostasis within 2 minutes, the procedure being repeated several times. Undisturbed the venom pledget preserved hemostasis for several hours. When it was dislodged during mastication a fresh venom pledget immediately controlled the ensuing hemorrhage. The patient's disease, however, continued unabated, although the external hemorrhage was controlled, and he died suddenly 2 months later, of a cerebral hemorrhage.

CASE 2.—*Hemophilia*. H. G. (Hosp. No. 178039), male, aged 28, first admitted in February, 1935, gave a history of hemophilia, typical but for normal coagulation time. His maternal grandfather was a bleeder, and the patient was told that the "bleeding disease" was rampant in this grandfather's family. The patient has 2 brothers, 1 of whom is a bleeder. At circumcision, at tonsillectomy, and at tooth extractions, dangerous hemorrhage occurred, each one lasting for weeks. Three years ago he bled for 16 days after a slight laceration of his gum, requiring a transfusion. On admission blood examination showed a normal coagulation time (5 minutes by the Lee and White method), and the patient stated that the coagulation time had always been normal despite his bleeding episodes. The Howell prothrombin-time was 40 minutes, as compared to a normal control of 22 minutes. All the other hematologic tests were normal.

The upper left third molar was removed with novocain and adrenalin anesthesia, and the area curetted. The first bleeding occurred 8 hours later. An interdental gauze packing failed to stop the bleeding. Then tiger-snake venom was applied on cotton without pressure for 10 minutes. A clot formed quickly, but was dislodged by the pressure of the escaping blood. This procedure was repeated 3 times without success. Then a venom pledget was applied, and pressure was maintained for 10 minutes with a gauze packing between the locked jaws. Bleeding ceased within the 10 minutes. Patient was awakened 4 hours later by recurrent bleeding. Again venom with pressure stopped the flow within 10 minutes. Four hours later hemorrhage again recurred, being controlled within 5 minutes by a venom pledget covered by an interdental gauze pack. This time the jaws were prevented from separating during sleep by a firm Barton bandage. There was no further bleeding until 7 hours later when the packing, venom-pledget, and clot were deliberately removed. Bleeding then recurred and was immediately stopped with a venom pledget covered by an interdental pack. No further bleeding occurred for 36 hours, when a slow ooze started, controlled intermittently by plain gauze packing without venom. This was followed by a larger flow which did not yield to plain gauze packing, but was stopped by the use of venom in 3 minutes. On each of the next 2 days, one packing with venom was sufficient to control the ooze. Patient was discharged 9 days after extraction, with the wound healing very well.

Nine days after his discharge, the patient, quite enthusiastic about tiger-snake venom therapy, asked to be readmitted for the extraction of two other diseased teeth. With his permission elaborate controls of other hemostatic devices were planned before venom should be employed. The patient was unusually cooperative, and even in the face of copious hemorrhage and while his hemoglobin was dropping rapidly, he insisted that we methodically exhaust our control methods before resorting to venom therapy.

On March 18, 1935, under novocain and adrenalin infiltration anesthesia, the lower left first molar and the upper right lateral incisor were evulsed. In addition, an alveolar flap was made at the base of the incisor for removal of a cyst. Three hours after the operation a slight ooze began, lasted 12 hours, barely tinting the saliva, and subsided without treatment. No bleeding occurred on the second and third days. On the fourth day oozing recurred and increased for 9 hours. A series of plain gauze packings failed to control the flow, so a packing steeped in a supersaturated tannic acid solution in 95% alcohol was applied. The hemorrhage soon diminished, and within 30 minutes had ceased.

On the fifth day, after 9 hours of intermittent bleeding, increasing in spite of plain gauze compresses, tannic acid gauze with interdental packing and a Barton bandage again produced hemostasis within 30 minutes. Two hours later hemorrhage recurred, but after 3 hours of futile gauze packings similarly responded to the tannic acid application with pressure.

On the sixth day, after an hour of bleeding, an adrenalin sponge diminished the flow temporarily, but 1 hour later profuse hemorrhage began from the three operative sites. Each of these received packs medicated at different times with tannic acid, gallic acid, ferric chlorid, and adrenalin. The bleeding became serious in spite of these measures. Finally venom was applied with pressure to the lower molar socket, which was bleeding dangerously. Within 3 minutes the flow from this site had stopped. The other two bleeding areas continued to flow unabated in spite of the other expedients. One hour later venom compresses stopped these two hemorrhages within 3 minutes. The two tooth sockets did not bleed thereafter.

It was noted at this time that a precipitated black incrustation of tannic acid and ferric chlorid had formed over the incision in the gum. On the 7th and 8th days bleeding occurred from the incision sporadically. On 2 occasions it did not respond to venom therapy promptly, subsiding only after 30 or 40 minutes. On the ninth day venom stopped the bleeding from the incision promptly after other methods failed.

On the tenth day bleeding from incision became serious again. It proceeded for 10 hours in spite of venom and other drugs. Finally, the entire bleeding area at the site of the incision was carefully denuded of the leathery black incrustation which formed a coating over it. A venom packing was applied to the raw and vigorously bleeding surface, and the hemorrhage ceased within 3 minutes. No further bleeding took place from the incision until the 14th day when profuse hemorrhage recurred. Because of the patient's anemia no preliminary controls were employed at this time. Bleeding ceased within 2 minutes after the application of venom (after 2 hours of hemorrhage). On the 15th day an ooze stopped spontaneously in 10 minutes. On the 16th day after 30 minutes of profuse flow venom therapy was followed within 2 minutes by hemostasis. Except for a slight ooze on the 17th day which stopped spontaneously in a few minutes, no further bleeding had occurred when the patient was discharged on the 24th day after operation. All the operative sites seemed well healed.

Case 3.—*Multiple Hereditary Telangiectases*. B. D., male, aged 55, realtor (treated by Dr. B. Seligman), gave the following family history: His mother, 2 sons, 1 daughter, and 20 nephews and nieces had had repeated, profuse hemorrhages, chiefly from the nose, in some cases from the tongue,

never from wounds of the skin. A brother had died of severe epistaxis. Almost all of them had had the onset of bleeding in adult life; 1 began to bleed in childhood.

For the past 20 years the patient had suffered from nasal hemorrhages, occurring about 4 times a week, usually lasting 5 or 6 hours. Examination showed multiple, generalized telangiectases, anemia, positive tourniquet test, no purpura, normal bleeding and clotting times, normal clot retraction, normal platelet count, and no abnormal blood cells.

The nasal hemorrhages rarely had yielded rapidly to pressure alone. The repeated use of adrenalin and especially of thromboplastin packings had produced hemostasis scarcely more promptly than had simple pressure, cessation occurring in about $\frac{1}{2}$ to 1 hour. Treatment of bleeding points with chromic acid had produced an increase in the frequency and severity of the epistaxis.

This patient, a relative of Dr. Seligman, has been using tiger-snake venom for $3\frac{1}{2}$ months, without medical supervision, being in Florida during this period. Epistaxis has occurred with equal frequency since tiger-snake venom therapy was initiated. The patient reports, however, that the hemorrhages have invariably yielded within 3 minutes after applying the venom. The loss of blood has been minimal. His weight, pallor, and general physical condition have greatly improved.

CASE 4.—*Essential Thrombocytopenic Purpura*. O. S., (Hosp. No. 169638) female, aged 14, has suffered from epistaxis for 9 years, and for the past 5 years purpura of the skin has occurred intermittently. Hematologic studies of the past 4 years during the periods of exacerbation of her disease have revealed secondary anemia, thrombocytopenia, prolonged bleeding time, delayed clot retraction, and positive tourniquet test.

On March 18, 1935, the lower right first molar was evulsed under nitrous oxid anesthesia. The postoperative bleeding was easily controlled by simple gauze packing. Fifteen hours later profuse hemorrhage set in and penetrated the packings. Packings of supersaturated tannic acid in 95% alcohol failed to influence the flow. After 2 hours of bleeding, unchecked by pressure of plain or of tannic acid packings, a tiger-snake venom compress was employed, and the bleeding ceased within 10 minutes.

On the second day a less severe hemorrhage was controlled by a tannic acid compress in 1 hour. On the fifth day a slight ooze occurred but subsided spontaneously. No further bleeding appeared.

On April 22, 1935, this patient returned to have the first and second upper left molar teeth extracted under nitrous oxid anesthesia. With one of the teeth adherent granulomatous tissue was evulsed. There were also multiple lacerations of the surrounding gum. A slight ooze occurred after the operation, and steadily increased during the succeeding 4 hours in spite of packings of cotton and plain gauze. A venom packing greatly diminished the flow, but did not stop it entirely. When the packing was removed 20 minutes later a solitary bleeding point was noted from beneath an everted lacerated fragment of the lateral alveolar margin. The interdental packing that had been used served only to lacerate this fragment further and to prevent its contact with the venom pledget. Another attempt to place venom in contact with this bleeding point was successful, digital pressure being employed on the venom pledget at this point for 5 minutes. Seven hours later severe hemorrhage recurred, again from the protruding fragment on the alveolar margin. Another venom pledget was carefully applied against the replaced alveolar fragment, and digital pressure maintained for 5 minutes. At the end of this time the resultant clot had firmly fixed the venom pledget to the wound, so that digital pressure could be released. The pledget was then held in place with gauze packing and a Barton bandage was applied. There was no further bleeding.

CASE 5.—*Essential Thrombocytopenic Purpura*. R. S. (Hosp. No. 178702), female, aged 23, gave a history of purpura of the skin, epistaxis, and bleeding gums for the past 8 months. Almost continuous epistaxis had been present for 3 weeks on admission. Hemoglobin was 26% (Dare), platelets 2000, bleeding time more than 30 minutes, clot retraction absent, tourniquet test strongly positive, leukocyte count normal. A transfusion was given after admission to the hospital on March 19, 1935. For 2 days after admission epistaxis continued from both sides of the nasal septum anteriorly. A rhinologist called in consultation was unable to diminish the flow of blood with plain packing, tannic acid packing, or adrenalin compresses. Finally, tiger-snake venom was used in packing the nose, and the flow stopped within 3 minutes. No nasal bleeding occurred for 36 hours thereafter. Then the nasal bleeding resumed. The entire left side of the septum appeared to be bleeding. Packing of the anterior nares with venom compresses failed to control slight bleeding posteriorly, and blood continued to ooze into the nasopharynx. No postnasal packing was performed. On the right side of the nose marked bleeding from Kiesselbach's triangle was stopped 2 minutes after the application of venom. On the same day a hemorrhage occurred from an abrasion in the external auditory canal of the right ear, and could not be stopped with plain packing or with tannic acid packing. Application of a venom compress stopped this source of bleeding within 3 minutes.

On the following day slight postnasal oozing persisted on the left side. On the sixth day splenectomy was performed under ether anesthesia. Later, slight nasal hemorrhage recurred but was controlled with plain gauze packing. A slight ooze from the abdominal wound was also noted, but controlled by plain gauze pressure. The patient developed a post-operative pneumonia, multiple lung abscesses, empyema, and died 16 days after admission to the hospital.

CASE 6.—*Hemophilia*. D. T. (Long Island Coll. Hosp. No. 1722, available through the courtesy of Dr. Tasker Howard), male, aged 25. Two maternal uncles of this patient had died in childhood of hemorrhage resulting from trivial external injury. The patient's bleeding tendency began soon after birth at circumcision. Recurrent hemarthroses, hematuria, hematomata, and prolonged hemorrhages from slight lacerations have occurred since infancy. Coagulation time of the blood in the past had varied between 30 and 50 minutes, but on present admission it has been between 8 and 17 minutes. No other hematologic abnormalities have been noted.

On March 22, 1935, the lower right second molar tooth was extracted. One hour later an oozing began which persisted intermittently for 12 days in spite of thromboplastin packings (renewed every 3 hours), adrenalin compresses, tannic acid dressings, and even electrocautery of the socket. After 12 days tiger-snake venom was applied to the socket, which had been bleeding through thromboplastin packings steadily for the previous 5 hours without signs of abatement. The bleeding stopped within 2 minutes. Seven days later a moderate oozing from the socket was again stopped within 2 minutes by venom. On the next day an ooze responded to venom with equal facility. No further bleeding occurred. The wound healed well.

CASE 7.—*Carcinoma of Head of Pancreas With Profound Jaundice*. B. L. (Hosp. No. 178852), male, aged 42, had an external biliary fistula created by cholecystostomy 6 months previously for obstructive jaundice due to carcinoma of the head of the pancreas. Intermittent jaundice had recurred since the operation because of blocking of the biliary fistula.

On the day before admission on March 25, 1935, severe epistaxis began, from both nostrils. Inability to control the hemorrhage led to his admission to the hospital. After futile attempts to control the hemorrhage with tannic acid and adrenalin packings, venom packings were employed. The bleeding ceased within 2 minutes.

CASE 8.—*Angioasthenia, with leech-bite hemorrhage.* M. B. (Hosp. No. 177514), female, aged 34, gives a history of previous prolonged postoperative hemorrhages (after surgical corrections of poliomyelitis deformities), a pronounced tendency to bruise easily, and occasional epistaxis (the last one lasting for 1 hour 2 days ago). She shows a pituitary type of obesity, purpuric spots in the skin, a markedly positive tourniquet test, normal bleeding and clotting times, no thrombocytopenia, and no abnormal blood cells.

After an operation on the right knee for suppurative arthritis she developed a thrombophlebitis of the right femoral vein. To the swollen and painful right thigh 5 leeches were applied on April 9, 1935. When the leeches had dropped off $1\frac{1}{2}$ hours later a continuous and increasing ooze appeared at the 5-leech marks. The blood from the leech wounds showed no tendency to clot, although blood drawn from the median basilic vein clotted normally. In spite of prolonged pressure with plain gauze dressings held in place with bandages and sand bags, the profuse flow persisted for 5 hours before local venom therapy was instituted. Venom compresses were employed on all 5 bleeding points. Complete cessation of hemorrhage occurred within 2 minutes. An hour later manipulation by the patient of the bandages dislodged one of the compresses, causing a recurrence of the flow. The blood which inundated the bandages and the bed now contained large firm clots. Reapplication of a venom compress again stopped the flow within 2 minutes. An hour later further manipulation of the bandages because of marked femoral pain aggravated by the pressure, stirred up a slight ooze of thick clotting blood, which subsided permanently with no treatment other than the application of moderate pressure.

Comment. Tiger-snake venom has been successfully employed to check uncontrollable local bleeding in 8 patients suffering from hemorrhagic tendencies, of which 3 cases were thrombocytopenia, 2 hemophilia, 1 of each multiple hereditary telangiectases, prolonged jaundice and angioasthenia with bleeding due to local action of hirudin from leech bites.

During the clinical experiments there were only 2 occasions when doubt arose as to the efficacy of the venom. On 1 occasion (Case 2) the failure seems to have been due to a thick coating of precipitated ferric chlorid and tannic acid, which interfered with the action of the venom. When this incrustation was removed and venom was applied to the raw bleeding surface, hemorrhage ceased within 3 minutes. On another occasion (Case 4) after the application of venom, a lacerated fragment of gum continued to bleed when the rest of the wound was dry. The ordinary interdental packing was serving only further to lacerate this fragment and to increase the hemorrhage from the site. The application of a venom pledget by digital tamponade to the exact point of bleeding promptly stopped the flow.

It has been interesting to observe a sort of rhythmic recurrence of the bleeding tendency in the hemophiliacs. After tooth extraction the socket is usually quite dry for 8 to 12 hours (the more so, of course, if adrenalin was mixed with the local anesthetic). Then after serious bleeding occurs and is checked by venom, it may recur about 24 hours later. In Case 2 bleeding recurred at about the same time in the afternoon for a number of days. Venom does not seem

to prevent recurrences of bleeding from the treated area after an interval of hours or days. Perhaps the renewed flow is due to actual trauma, such as chewing, or to the cryptic factors which influence the hemorrhage in a hemophiliac, or to the washing away or destruction of venom. To minimize the possibility of recurrent hemorrhage, pressure should be maintained over the site of bleeding for several hours after hemostasis has been attained. For dental hemorrhage a Barton bandage has been usually applied overnight.

Neurologic examination of these patients disclosed no evidence that the neurotoxin of the venom was doing any damage. Even in patients who received large amounts (15 to 30 cc. of 1/5000 solution) orally or intranasally, no impairment of the cranial nerves and no muscular weakness were noted.

Locally no swelling, ulceration, necrosis or infection was observed. The wounds healed normally.

Some confusion may arise between tiger-snake venom and the venom of the water-moccasin which has been used recently to prevent hemorrhage.¹¹ Moccasin venom is given intradermally or subcutaneously. Tiger-snake venom is to be employed only by topical application and is not to be injected.

Summary. 1. Tiger-snake venom in high dilution readily clots both normal and pathologic blood *in vitro*.

2. A simple arbitrary clotting unit is described in an effort to standardize various batches of venom and to detect deterioration in aging solutions.

3. In cases of active hemorrhagic disease, tiger-snake venom has produced prompt local hemostasis when common expedients (pressure, thromboplastin, tannic acid, adrenalin, ferric chlorid) have failed.

4. The minimal amounts of venom employed and its action in closing the channels of absorption by local thrombosis provide for it a therapeutic index within limits of safety.

5. It has not prevented recurrence of hemorrhage or otherwise affected the course of the hemorrhagic disease.

6. Its application is limited to accessible bleeding lesions, where it may be applied topically with pressure.

Conclusion. The venom of the Australian tiger-snake (*Notechis scutatus*) has been successfully employed by topical application to arrest severe hemorrhage from accessible lesions in 8 cases of blood dyscrasia.

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"TIGHT" (NON-REGURGITANT) MITRAL STENOSIS.

A CLINICO-PATHOLOGICAL STUDY.

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TIGHT (*i. e.*, non-regurgitant) mitral stenosis as a clinical condition has received little attention in the most modern and complete textbooks of cardiology, such as White's,¹ MacKenzie's², Vaquez's,³ Eden's,⁴ Romberg's,⁵ and others being mentioned in most cases merely as a pathologic curiosity. The scanty clinical description of this entity may explain why these cases come so often unrecognized to the autopsy table, surprising the pathologist with the unexpected extremely narrow mitral ostium. In most instances the condition clinically is believed to be a severe pulmonary infection or even a pulmonary neoplasm. Our interest was primarily aroused by a case of tight mitral stenosis (reported by us several years ago⁶) where the pulmonary signs were prominent and the rheumatic nature of the disease hidden, for the auscultatory findings over the mitral valve were entirely negative. Only the electrocardiogram was of some help, showing a high bifid *P* wave which made Dr. H. Vesell suspect the possibility of mitral stenosis. In the past 5 years, in which we have paid especial attention to this clinical

picture, we have had 13 such cases coming to autopsy at this hospital, the first 9 of which we have analyzed for this study. Of these 9, 5 were correctly diagnosed antemortem.

A careful study of these 9 cases convinces us that the condition is encountered frequently and clearly enough, especially in hospital practice, to deserve an autonomous status. The pathologic findings are distinct and uniform, indicating that a common clinical picture is associated with the entity. A description of the clinical course of the disease and the criteria by which this type of mitral stenosis can be diagnosed antemortem is the subject of this paper.

Beginning with the final picture, as it were, we find at autopsy as the key characteristic of the condition a slitlike, fibrosed and calcified mitral valve, so stenosed that a thin probe passes through it with difficulty, and so hard that it rings at the touch of the knife. The shape of the mitral opening varies—often it is “buttonhole,” sometimes funnel shaped, sometimes stellate—but in all cases it is extremely narrow. The term *tight* mitral stenosis is then a much more fitting one than the more limiting term, *buttonhole*.

The rest of the changes are all secondary to the marked stenosis of the mitral ostium. Because insufficient blood reaches the left ventricle through the narrowed valve to furnish normal amount of work, this chamber atrophies. In contrast the left auricle is very large, usually extends beyond the right border of the heart, and is often filled with thrombi. The right side of the heart, too, suffers from the extreme obstruction to the blood flow at the mitral valves and both the right ventricle and auricle are slightly hypertrophied and dilated. Quite distinctive of the condition is the fact that the cardiac lesions are almost uniformly accompanied by extensive pulmonary changes—pulmonary embolization, pulmonary infarction, pulmonary fibrosis, and sclerosis of the pulmonary artery (including at times the smaller pulmonary vessels).

The stenosis of the mitral valve is so marked at autopsy that it is immediately recognized as the cause of death, since the circulation cannot be maintained for any length of time through such an obstruction. This also means that a lesser degree of stenosis must have preceded the terminally severe narrowing. The exact pathologic state before the marked stenosis has occurred cannot be evaluated with certainty in our present state of antemortem examinations. The presence of a small, atrophic left ventricle would indicate, however, that the auricle at no time received a reflux of blood, *i. e.*, that functionally at least the mitral valve was stenotic and not insufficient. Clinically, too, the patient shows the persistent symptoms, the failure at compensation and the poor reaction to treatment which distinguishes the case of pure mitral stenosis from the milder one of double mitral disease (stenosis and insufficiency). These pathologic and clinical considerations allow us to assume with some reason that the lesion began as a pure mitral stenosis without

accompanying insufficiency, or at least with the stenosis predominating over the insufficiency and that recurrent inflammatory changes took place in the valve to bring about a greater narrowing of the ostium. Of course, the possibility cannot be absolutely excluded that in the milder degree of stenosis there was a temporary insufficiency. In the younger individual the change is probably inflammatory and is connected with recurrences of the rheumatic infection. In the middle-aged period and later in life the fibrosis and deposition of lime in the mitral valve forms part of the general sclerotic process, but careful pathologic examination always shows that these mitral valves have been previously affected by the rheumatic virus. The arteriosclerotic process then is superimposed on the rheumatic in older individuals. In any case once the fibrosis and calcification has narrowed the mitral valve sufficiently, irreversible decompensation sets in, treatment is of no avail, and the patient falls a victim to the mechanical block in the circulation.

A summary of the 9 cases upon which this concept of the disease is based follows.

Case Reports. CASE 1.—Miss I. M. (No. 47054), aged 21, admitted to the service of Dr. A. A. Epstein, March 15, 1932, died March 17, 1932.

History. The patient gave no history of rheumatic fever or other rheumatic manifestations. On routine school examination in September, 1928, she was told she had a heart murmur. Soon after this she suffered from exertional dyspnea, cough and blood-streaked expectoration for a period of 3 months. She was feeling fairly well after that until December, 1929, when she complained of chilliness, palpitation, and recurrent attacks of precordial pain, unrelated to exertion, radiating to the left shoulder, and lasting about 10 minutes. Pallor and weakness increased for several months, so that on first admission to this hospital in May, 1930, she was suspected of having subacute bacterial endocarditis. No definite evidence for this could be obtained however. She showed at this time (May, 1930) a mitral lesion and pulmonary congestion, and was discharged improved but not fully compensated. She failed to regain complete compensation in the 2 years that followed. Five days before the present admission she began to complain of cough, sharp pains in the lower chest and bloody expectoration, and had a shaking chill 3 days later.

Physical Examination. Temperature, 104°; pulse, 124, thin; Respiratory, 32; blood pressure, 85/50. The patient looked acutely ill, markedly dyspneic and cyanotic. There was dullness, diminished breath sounds and numerous moist râles at the right base. The heart was enlarged, the first heart sound short and snappy. A double mitral murmur and thrill were present at the apex. P2 was markedly accentuated. The liver was felt 2 fingers below the costal margin; the spleen barely palpable.

Laboratory Findings. Urine negative. White blood cells, 23,200; 91% polys. Electrocardiogram. Right axis deviation. Large, slurred P waves in Lead II.

Course. The temperature rose the following day to 106.4°. In spite of oxygen and supportive treatment, the patient developed pulmonary edema and died.

Clinical Diagnosis. Decompensated mitral valvular disease. Bronchopneumonia. Pulmonary edema.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Marked dilatation of left auricle. Small left ventricle.

Hypertrophy and dilatation of right ventricle. Dilatation of right auricle. Terminal verrucous endocarditis of tricuspid valve. Atheromatosis of right coronary artery (slight) and of pulmonary arteries (moderate). No Aschoff bodies microscopically. Bronchopneumonia, right lung. Pulmonary edema.

Comment. In this case, about 2 years before exitus, the patient developed dyspnea on slight exertion and pulmonary congestion, without any recurrent infection. At first treatment would influence her more or less favorably, but did not bring about actual return to compensation. The periods of relief would become less and less frequent, and the pulmonary congestion and stasis more and more marked until a terminal bronchopneumonia complicated the mitral valvular disease and brought about the fatal outcome. Periodically the patient had pains simulating angina pectoris, a condition not uncommon in many cases of mitral stenosis, particularly where the left auricle is extremely enlarged, as pointed out by Morawitz.⁷ This explains why the anginal syndrome is more often present in tight mitral stenosis, where the left auricle attains a marked degree of distention, than in other forms of mitral disease. It is reasonable to assume that the patient started with a pure mitral stenosis and progressed to an absolute stenosis, as evidenced by the small, atrophic left ventricle. The marked progressive narrowing caused damming back of the blood in the lesser circulation, and led to terminal bronchopneumonia and pulmonary edema.

CASE 2.—Mr. S. F. (No. 59465), aged 23, admitted to the service of Dr. I. W. Held on November 24, 1933, died November 25, 1933.

History. The patient had scarlet fever during early childhood, and rheumatic fever at 10 years. At this time he developed aortic stenosis and mitral stenosis. He recovered sufficiently to go through college and qualify as a teacher. However, from the age of 11 until he took sick with terminal pneumonia, he complained of shortness of breath, frequent spasmodic cough and occasional expectoration of tenacious sputum. In addition to the valvular disease, he had signs of bronchitis and emphysema, but at no time any evidence of decompensation. About 6 weeks before admission the patient was ill with Type I lobar pneumonia. With the aid of serum, he recovered completely and was well enough to be permitted back to work by the fourteenth day. He continued well for about a month. The day before admission, however, he suddenly became very ill, developed fever, pain in the left chest aggravated by breathing, cough and expectoration of blood-streaked sputum.

Physical Examination. Temperature, 103°; pulse 100, thin; respirations, 32; blood pressure, 106/70. The patient appeared acutely ill, moderately cyanotic, somewhat drowsy. Breathing was rapid and difficult. Tracheal râles were heard coming from the throat. There were numerous moist râles throughout both lungs. The heart was enlarged, especially to the left, the apical impulse abnormally forceful. There was a presystolic and a systolic murmur at the apex, and a harsh systolic murmur in the aortic area, accompanied by a thrill. The second aortic sound was not heard, the liver and spleen not palpable. There was no edema.

Laboratory Findings. Urine and blood, negative.

Course. The patient's condition was critical from the start. He was digitalized and put under an oxygen tent; a phlebotomy of 500 cc. was performed—all to no avail. In 23 hours he died.

Clinical Diagnosis. Chronic cardiovalvular disease. Tight mitral stenosis. Aortic stenosis. Bilateral bronchopneumonia. Pulmonary edema.

Anatomic Diagnosis, Condensed (Dr. A. Plaut). "Buttonhole" mitral stenosis. Stenosis of aortic and tricuspid valves. Verrucous endocarditis of tricuspid valve (terminal). Hypertrophy of heart. Old and recent rheumatic carditis, as evidenced microscopically by large number of scars and Aschoff bodies. Multiple areas of bronchopneumonia. Obliterating bronchiolitis.

Comment. This case is included, although not showing the typical clinical picture of the terminal decompensation of tight mitral stenosis, because we believe that of the 3 valvular lesions this patient had, it was the "buttonhole" mitral stenosis which influenced to a large extent the course of the disease (even when he was fully compensated) and eventually caused the fatal termination. It was responsible for the patient's chronic recurrent pulmonary symptoms, such as frequent cough and dyspnea, and also the obliterating bronchiolitis. It is our impression furthermore that the bronchopneumonia terminated with fatal pulmonary edema in so short a time largely because of the "buttonhole" mitral stenosis, for there were no signs of toxicity or sepsis which would otherwise cause the fatal outcome. The recent Aschoff bodies might be interpreted as showing that a recurrent rheumatic carditis was likewise present. It is very likely however that if the tight mitral stenosis had not caused the bronchopneumonia to terminate fatally the patient would have developed acute rheumatic carditis, activated by the recent pulmonary infection, and would have given clinical signs of this later.

CASE 3.—Mr. I. G. (No. 58550), aged 29, admitted to the service of Dr. M. A. Rothschild, October 17, 1933, died October 19, 1933.

History. The patient had rheumatic fever with migratory joint pains 13 years ago. Eight years later he was refused life insurance because of rheumatic heart disease. He was nevertheless symptom-free until 1½ years ago when dyspnea and persistent cough set in, to be followed by edema of the legs 4 months later. These symptoms increased steadily. The patient had been under careful medical supervision and had received 1½ to 4½ grains of digitalis daily for 6 weeks prior to admission. In spite of this he remained decompensated. He noticed jaundice a week before, and blood-streaked sputum a day before admission.

Physical Examination. Temperature, 100.2°; pulse 98, fair; respiration, 32; blood pressure, 132/96. The patient was acutely ill, pale, dyspneic, orthopneic. His lips, ears and extremities were cold and cyanotic. The lungs showed dullness at both bases posteriorly with moist râles and diminished breath sounds. The cardiac apex was in the anterior axillary line in the 7th interspace. A loud systolic and rough diastolic apical murmur were heard; P2 was louder than A2; the rhythm distinctly coupled. The liver was felt pulsating 5 fingers below the costal margin. There was no evidence of ascites, although the extremities and scrotum were edematous.

Laboratory Findings. Urine. 3+ albumin, with occasional granular casts. Blood and sedimentation rate normal. Circulation time 51 seconds. Electrocardiogram. High, wide, notched P waves in Leads I and II. Raised RS-T segment in Lead I. Occasional ventricular premature contraction.

Course. Phlebotomy brought temporary relief; but the patient had a sudden attack of extreme restlessness and dyspnea on the second day. He rapidly became pulseless, and within 3 hours died.

Clinical Diagnosis. Chronic cardiovascular disease. "Buttonhole" mitral stenosis. Relative tricuspid insufficiency.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Dilatation of right ventricle and left auricle. Verrucous endocarditis of aortic valve. Chronic endocarditis of tricuspid valve. Atheromatosis of pulmonary vessels. Fibrosis of lungs.

Comment. In summary this patient presented the picture of persistent pulmonary symptoms and signs for almost $1\frac{1}{2}$ years, such as dyspnea, cough, bloody expectoration, and progressive decompensation with edema. Even though he showed clinical evidence of tricuspid insufficiency (jaundice, large liver) the opening up of the tricuspid valve did not relieve his dyspnea because it was largely due to persistent, progressive pulmonary changes, such as pulmonary fibrosis. The decompensation in this case was prolonged, the symptoms persisting in spite of careful treatment (digitalis, etc.). Note that the electrocardiogram showed very high, wide and notched P waves, a finding which may be related to sclerosis of the pulmonary vessels and fibrosis of the lungs.⁸

CASE 4.—Miss A. S. (No. 43510), aged 34, admitted to the service of Dr. M. A. Rothschild, September 2, 1931, died September 4, 1931.

History. The patient had rheumatic fever at 3, 10, 15, 22, and 26 years. She had no cardiac complaints until 5 months before admission, when she first experienced shortness of breath and palpitation on exertion. From that time she became more and more incapacitated. In the last month a cough productive of blood-streaked sputum appeared, and the feeling of tiredness became more prominent.

Physical Examination. Temperature, 100°; pulse 100, Corrigan; respiration, 32; blood pressure, 150/34. The patient was very cyanotic and dyspneic. Numerous moist crackling râles were heard throughout both lungs. The heart was markedly enlarged, especially to the left. A systolic and diastolic murmur were heard at the apex, and a soft diastolic murmur at the base. The liver was palpable and tender 5 fingers below the costal margin. Moderate pretibial edema and some clubbing of the fingers were present.

Laboratory Findings. Urine and blood negative.

Roentgen Ray. Markedly enlarged heart, with the contour of combined mitral and aortic lesions.

Course. The patient failed to respond to digitalis therapy. She died in her sleep rather suddenly the second morning after admission.

Clinical Diagnostic. Chronic cardio-valvular disease. Mitral stenosis and insufficiency. Aortic insufficiency.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis, showing microscopically calcific deposits within hyalinized fibrotic areas. Acute and chronic verrucous endocarditis of mitral and aortic valves. Concentric hypertrophy of all chambers of the heart. Marked hypertrophy with moderate dilatation of left ventricle. Aortic insufficiency. Acute verrucous endocarditis of left auricle. Pulmonary artery sclerosis. Pulmonary fibrosis. Chronic passive congestion. Early cardiac cirrhosis of liver.

Comment. In this case although there were multiple valvular lesions present and even evidence of acute changes in the valves and left auricle, one can state definitely that the aortic regurgitant lesion in itself was not responsible for the sudden decompensation, or the fatal outcome. In fact it was the very tight "buttonhole" mitral stenosis with marked pulmonary congestion, pulmonary fibrosis, and pulmonary artery changes in a relatively young person which caused the sudden terminal cardiac failure. This case exemplifies the dictum that a double valvular lesion, once decompensated goes more readily to fatal termination than a single one, especially if one of the lesions is of the tight mitral stenosis type.

CASE 5.—Mrs. R. D. (No. 51586), aged 35, admitted to the service of Dr. I. W. Held, October 23, 1932, died October 26, 1932.

History. The patient gave no history of rheumatic fever. She knew of her heart disease for 5 years before admission, during which time she suffered almost constant dyspnea and some orthopnea. She also had occasionally attacks of chest pain with substernal discomfort. On the day before admission there was an acute onset of fever, chills, pain in the left chest, cough and bloody expectoration.

Physical Examination. Temperature, 101.6°; pulse 116, fair; respiration, 36; blood pressure, 108/60. The patient was markedly cyanotic. There were numerous rhonchi heard throughout the chest, with dullness and crepitant râles at the left base. The heart was enlarged, the sounds weak and distant. A presystolic rumble was heard at the apex. P2 was markedly accentuated and reduplicated, suggesting gallop rhythm. The liver was palpable 3 fingers below the costal margin. There was no edema.

Laboratory Findings. Urine 2+ albumin, occasional granular cast. Red blood cells, 3,700,000; hemoglobin, 68%; white blood cells, 47,200; 92% polys. Sedimentation rate 60 mm.% in 45 minutes. Sputum: Type IV of pneumococcus.

Roentgen Ray. Consolidation of central portion of left lung and base of right lung. Mitral configuration with congestion of lungs due to decompensation.

Electrocardiogram. Split P waves in all leads. Diphasic T₂ and inverted T₃.

Course. The temperature rose steadily; the consolidation spread until it involved the entire left lung. Exitus occurred on the third day.

Clinical Diagnosis. Chronic cardiovalvular disease. Mitral stenosis. Lobar pneumonia, left lung.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Retraction of aortic valves with recent verrucous endocarditis. Dilatation and hypertrophy of left auricle and ventricle. Moderate hypertrophy of right ventricle. Old and recent endocarditis of the tricuspid valve. Fatty changes in myocardium. Rusty color of right lung. Cheesy tuberculosis of hilar lymph nodes. Red hepatization of almost the whole left lung with diffuse fibrinous pleuritis. Stasis in spleen and liver.

Comment. For about 5 years this patient suffered from dyspnea, orthopnea and occasional attacks of suffocation simulating asthma. These symptoms, uninfluenced by treatment, were due to the persistent pulmonary congestion, bronchitis and emphysema secondary to disturbance of the pulmonary circulation in tight mitral stenosis. When pneumonia set in toward the end, the unfavorable dynamics

of the heart due to the "buttonhole" mitral stenosis led rapidly to cardiac failure and death. The slight verrucous deposits on the aortic and tricuspid valves are terminal and as such are found at autopsy in many cases of cachexia, severe infections, etc. In this case the persistent symptoms and physical signs pointing to pulmonary embarrassment (such as the marked accentuation and reduplication of the pulmonic second sound at the base simulating gallop rhythm) suggested the clinical diagnosis of "buttonhole" mitral stenosis.

CASE 6.—Mrs. S. B. (No. 61630), aged 37; admitted to the service of Dr. M. A. Rothschild, February 23, 1934, died February 25, 1934.

History. The patient had an attack of rheumatic fever at 24. She had no symptoms until about 2 years ago when she noticed difficulty in catching her breath on exertion. There was an interval of relative well-being until 6 weeks before admission when the patient had pain in the left chest and an increase in her shortness of breath. One week before admission she noticed swelling of the legs, cough and bloody expectoration.

Physical Examination. Temperature, 100°; pulse 100, small; respiration, 46; blood pressure, 110/50. The patient was exceedingly ill, dyspneic, cyanotic and orthopneic. There was a loud, harsh systolic murmur in the third left interspace accompanied by a systolic thrill. A distinct systolic murmur was heard at the apex transmitted to the axilla; but no definite diastolic murmur. The first sound at the apex was short. Auricular fibrillation was present with an apical rate of 150 and a pulse rate of 100. At the left base there was an area of bronchial breathing, dullness and coarse, moist râles. The liver was palpable 4 fingers below the costal margin. There was pitting edema of both lower extremities and back.

Laboratory Findings. Urine, sedimentation rate and circulation time normal. Venous pressure 22 cm.

Electrocardiogram. Q-R-S complexes of low voltage in all leads.

Roentgen Ray. Effusion in lower portion of left pleural cavity with some deviation of the heart and mediastinum to the right. Heart shape that of double valvular disease with very marked left auricular enlargement.

Course. In spite of rapid digitalization, the rate continued to be high. Phlebotomy of 350 cc. as well as thoracentesis of 1000 cc. of dark brown fluid from the left chest were of no avail. The patient became wildly irrational and died on the third day after admission.

Clinical Diagnosis. Chronic cardiovalvular disease. "Buttonhole" mitral stenosis. Aortic stenosis? Aortic insufficiency? Pulmonary infarction.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). Old and recent rheumatic mitral endocarditis with "buttonhole" stenosis. Thrombosis of left auricle and right auricular appendage. Old and recent aortic endocarditis with insufficiency and stenosis. Hypertrophy of right ventricle. Distention of both auricles. Perivascular scars and occasional small Aschoff bodies in myocardium microscopically. Atheromatosis of pulmonary vessels. Emboli of lung vessels. Large infarct, left lung and lower lobe of right lung. Serofibrinous pleuritis. Infarcts of kidneys and spleen. Nutmeg liver.

Comment. As in many of our cases of "buttonhole" mitral stenosis, this patient had an additional valvular lesion—the double aortic. Roentgen ray, autopsy and clinical evidence all indicated however that the cardiodynamics were determined almost exclu-

sively by the tight mitral stenosis. Roentgenologically, the configuration was mitral, not aortic. Anatomically, the left ventricle was not enlarged as in cases of aortic valvular disease. Instead, the right ventricle and auricles were hypertrophied and the pulmonary arteries sclerosed. Clinically, too, the picture was typically mitral. The first symptoms were those of stasis in the lungs due to interference with the pulmonary circulation. After a period of relative well-being, progressive decompensation with pulmonary infarcts and general anasarca developed. The heart could have gone on for a long time without decompensation were it not for the "buttonhole" mitral stenosis.

CASE 7.—Mr. A. B. (No. 54102), aged 39, admitted to the service of Dr. I. W. Held March 9, 1933, died March 14, 1933.

History. The patient had chorea at 3 years. For the past 17 years he has had dyspnea on exertion and more recently orthopnea. He was able to continue work as an artist until 2 years ago when ankle edema developed. At this first admission to this hospital, the condition was diagnosed as mitral stenosis and insufficiency, auricular fibrillation, moderate decompensation. With rest and digitalis he improved considerably; the edema disappeared. At home, despite employment of salyrgan and digitalis, edema of the lower extremities would make its appearance from time to time. He tired easily, and was practically an invalid the last few months. The weakness and edema increased a few weeks before admission.

Physical Examination. Temperature, 99.6°; pulse 100, fair; respiration, 26; blood pressure, 120/70. The patient was a slightly orthopneic, dyspneic man, not appearing severely ill. The lungs were clear. A long systolic, and a short diastolic murmur with a snappy first sound were heard at the apex. P2 was accentuated and reduplicated. Auricular fibrillation was present with an apical rate of 120 and a pulse rate of 108. The liver was felt 4 fingers below the costal margin, tender and pulsating. There was moderate ankle and pretibial edema.

Laboratory Findings. Urine 3+ albumin, frequent hyalin casts. Blood and sedimentation rate normal. Venous pressure 14 cm. Circulation time 40 seconds.

Course. The patient appeared to be fairly comfortable. His edema failed to react however to intensive digitalization. On the fifth day he took a sudden turn for the worse, and complained of overpowering weakness and shortness of breath. He showed signs of rapidly increasing decompensation. Numerous râles were heard throughout the lungs, evidencing the onset of pulmonary edema, and 15 hours later he died.

Clinical Diagnosis. Chronic cardiovalvular disease. Tight mitral stenosis. Ball-valve thrombus of left auricle?

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Distention of auricles. Large thrombus in left auricle. Dilatation and hypertrophy of right ventricle. Atrophic left ventricle. Severe atherosclerosis of pulmonary arteries with sclerosis to lesser degree of smaller pulmonary vessels. Edema of lungs. Stasis in spleen, kidneys and liver.

Comment. Although on previous admission, due to the systolic murmur, this patient was believed to have both mitral stenosis and insufficiency, the entire clinical picture speaks for the predominance of the stenotic over any possible insufficiency lesion. The atrophic left ventricle indicates that the mitral stenosis must have been

"tight" from the start, and explains why the patient was never perfectly comfortable and had dyspnea on exertion for fully 17 years. When the stenosis became more advanced in the last 2 years of the patient's life, the edema became more prominent and did not respond to treatment. Auricular fibrillation finally led to a sudden termination as the result of auricular thrombosis.

CASE 8.—Mrs. A. Z. (No. 55771), aged 42, admitted to the service of Dr. M. A. Rothschild, May 29, 1933, died June 15, 1933.

History. In 1923, at 32 years, the patient had polyarthrititis. She was not aware of any cardiac involvement until 4 years ago, when she had polyarthrititis, fever and marked dyspnea. Since then she was never fully compensated, her legs being always edematous to a greater or lesser extent. She was able to do her household tasks with difficulty until 8 months before admission, when she developed dyspnea, orthopnea, weakness, and occasional attacks of severe precordial pain. These symptoms continued until admission.

Physical Examination. Temperature, 100°; pulse 80, poor; respiration, 30; blood pressure, 100/60. The patient was acutely ill, markedly cyanotic, dyspneic and orthopneic. The heart was enlarged to the left, and had a loud presystolic and systolic murmur at the apex, with markedly accentuated P2. The liver reached 8 fingers below the costal margin, was tender and pulsating. There was pitting edema of the lower extremities.

Laboratory Findings. Urine, blood and sedimentation rate normal. Venous pressure 20 cm. Circulation time 28 seconds.

Electrocardiogram. Sinus arrhythmia. Inverted T₁. Another electrocardiogram shortly before exitus showed a wandering pacemaker.

Course. The patient received large doses of digitalis and salyrgan; phlebotomy was performed several times—all to no avail. The patient died in about 2 weeks.

Clinical Diagnosis. Chronic cardiovalvular disease. Tight mitral stenosis.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Hypertrophy and dilatation of right ventricle and left auricle. Small left ventricle.

Comment. It is known from the history that for fully 6 years after the first attack of rheumatic fever the patient was not aware of any cardiac symptoms. It is not possible to state whether the first rheumatic attack left the valves perfectly intact or, what we think more likely, that they were injured so mildly as not to have interfered with the cardiodynamics. The second rheumatic attack however probably caused marked narrowing of the mitral ostium. Because of this the patient was never comfortable for the 4 years to follow, and progressed uninterruptedly, uninfluenced by treatment, to a fatal decompensation.

CASE 9.—Mr. D. O. (No. 38482), aged 47, admitted to the service of Dr. A. A. Epstein, December 10, 1930, died January 8, 1931.

History. The patient had rheumatic fever at 27 and again at 41. One year after the second attack (5 years ago), he began to have occasional shortness of breath and ankle edema. He was hospitalized 4 months prior to the present admission because of attacks of nocturnal paroxysmal dyspnea and recurrent ankle edema. The findings then were mitral stenosis, aortic insufficiency and auricular fibrillation. He was discharged improved.

Although not completely compensated on 6 grains of digitalis daily, he felt fairly well until 3 weeks before admission when he began to have recurrences of his nocturnal attacks of dyspnea.

Physical Examination. Temperature, 100°; pulse 80, thin; respiration, 35; blood pressure, 116/72. The patient was very cyanotic, dyspneic and slightly jaundiced. His respirations were of asthmatic character. There were numerous rhonchi throughout the chest, and diminished breathing at the right base. The apex was seen and felt in the anterior axillary line. The first heart sound was snappy and associated with a systolic murmur. Auricular fibrillation was present with an apical rate of 180 and a pulse rate of 80. The liver was just palpable; the ankles slightly swollen.

Laboratory Findings. Urine, blood and sedimentation rate normal. Venous pressure 21 cm. The icteric index varied between 20 and 25.

Electrocardiogram. Auricular fibrillation. Marked splintering of Q-R-S complexes in all leads.

Roentgen Ray. Cardiac decompensation with pleural effusion at right base.

Course. The patient became less cyanotic, and the edema of the legs subsided during the first week (after salyrgan injection). On the eighth day, however, he had violent pains in the right lower chest, bloody expectoration and rise in temperature to 103°. There were clinical and Roentgen ray signs of infarction at the right base. Seventeen hundred and fifty cubic centimeters of serosanguinous fluid were removed by paracentesis from the infarcted area a few days later. Signs of pyopneumothorax developed rapidly. He became progressively more cyanotic, dyspneic and edematous until death ensued about a month after admission.

Clinical Diagnosis. Chronic cardiovalvular disease. Mitral stenosis. Pulmonary infarct with secondary pyopneumothorax, right side.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Old and recent mitral endocarditis. Aortic valves drawn out by scar formation between the mitral valve, and the septum. Recent thrombus partly obliterating mitral orifice. Parietal thrombosis in both distended auricles. Hypertrophy of right ventricle. Purulent infarct in lower lobe of right lung with basal empyema. Adhesions at both apices. Old infarcts in spleen and left kidney. General stasis.

Comment. The postmortem findings indicate that the main brunt of the disease was in the mitral valve in the form of a tight mitral stenosis. The aortic valve showed evidence of chronic endocarditis, but not marked to any great extent. Neither a high pulse pressure nor Corrigan pulse were present to suggest that the aortic valvular disease had much to do with the disturbed dynamics of the heart. The clinical course after the second attack of rheumatic fever speaks for greater narrowing of the mitral stenosis that already existed, causing a decompensation which was only slightly influenced by treatment and progressed rapidly to a fatal termination. The narrowing in this case of fibrillation resulted in multiple pulmonary infarcts, one of which became infected and led to a purulent pleural effusion.

Comment. Description of "tight" mitral stenosis as a clinical entity encounters the difficulty that the valvular lesion is often in the background, and the pulmonary signs in the foreground. Still a careful clinical study of the case, taking into consideration the

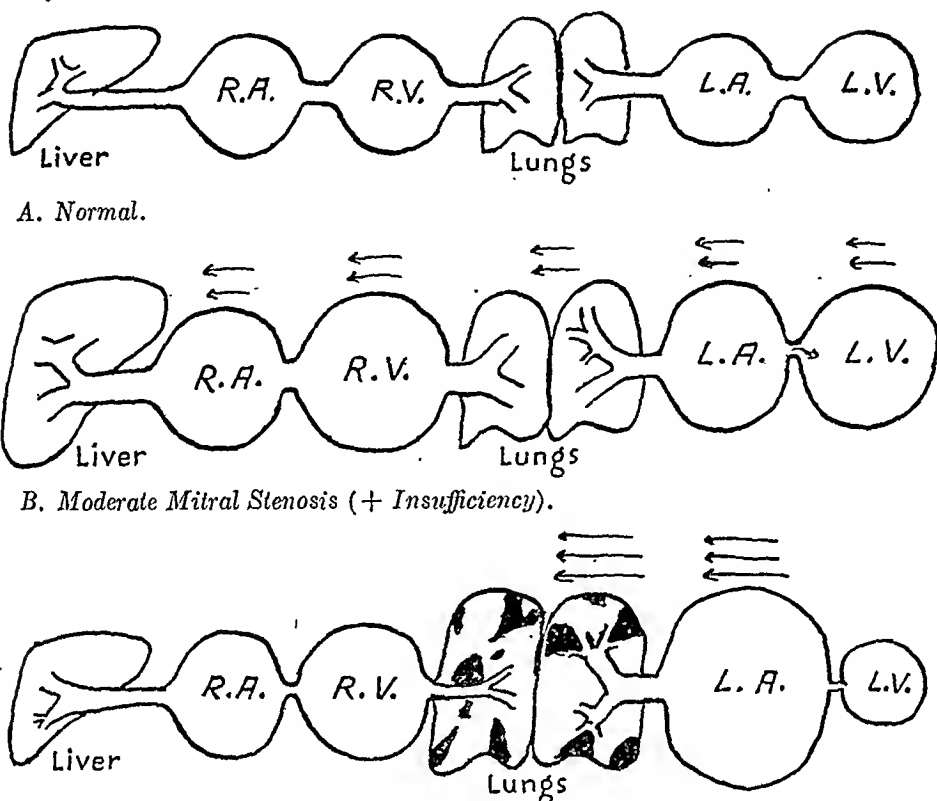
previous history, especially as regards circulatory status, should enable one to establish the proper diagnosis with the exception of those cases brought to the hospital *in extremis*, or where the pulmonary signs are so prominent as to mask entirely the underlying condition. That the diagnosis is possible is attested to by the fact that 5 of the 9 cases here reported were correctly diagnosed antemortem, as well as all of the 4 later cases not reported here. What are then the guiding diagnostic phenomena?

Since the condition starts as a mitral stenosis without an accompanying insufficiency, it is important to give the clinical characteristics of the pure mitral stenosis group, especially those which distinguish it from the more common double mitral involvement. We can thus learn to recognize those cases which are fertile soil for the development of a tight mitral stenosis.

It is well known that in every mitral stenosis there is excessive strain on the left auricle and the pulmonary circuit, and a reduced blood inflow into the left ventricle. When insufficiency accompanies the stenosis, the narrowing is not as severe, and more blood reaches the left ventricle. The resulting hypertrophy of this chamber permits more blood to be pumped into the greater circulation, thus relieving any additional strain on the pulmonary circulation. In contrast in the case of pure mitral stenosis there is more narrowing and a greater strain on parts of the heart which are unable to bear the load, as Figure 1 shows. The blood reaching the left ventricle in these cases is so reduced in amount that left ventricle atrophy with consequent undernourishment of the heart and other body tissues results. This reduced left ventricular output shows itself clinically in the easy fatigability, the cold extremities, the thin pulse and the short snappy character of the first heart sound. Roentgen ray also shows *very early* in the course of these cases a mitral configuration with prominent pulmonary artery shadow, a dilated left auricle often extending so far to the right as to form the right upper cardiac border, and an enlarged right ventricle which pushes the small left ventricle outward to the left (Fig. 2). When the left auricle is much enlarged the barium-filled esophagus is found to be pushed to the right and also backward (by the anteriorposterior enlargement) as Brown and McCarthy have recently reported.⁹

The back-pressure chronic passive congestion which is part of all mitral disease is much more severe in the case of pure mitral stenosis than in double mitral affection. Because of its greater severity and persistence, chronic irreversible pulmonary changes, such as pulmonary fibrosis, pulmonary infarction, and sclerosis of the larger and smaller pulmonary vessels occur. According to Monterde,⁸ the pulmonary hypertension with consequent arteritis is responsible for the high, bifid *P* waves which the electrocardiogram often shows in these patients. Clinically the severe pulmonary

stasis is expressed as persistent pulmonary complaints and a markedly accentuated and reduplicated pulmonic second sound.



C. Tight Mitral Stenosis.

FIG. 1.—Diagram illustrating the difference in the changes produced by moderate mitral stenosis with regurgitation and those of marked stenosis of the pure non-regurgitant type—tight mitral stenosis. The upper third (A) shows the normal relationship of the heart chambers to each other, and the pressure relationships in the lungs and the large venous bed of the liver. In moderate mitral stenosis (B) the left ventricle takes some of the load off the left auricle by regurgitation. The increased pressure in the left auricle is transmitted through the congested lungs to the right ventricle, which is consequently much enlarged. The load can further be taken off the enlarged right ventricle by the tricuspid valve which, becoming incompetent, permits the large veins and the liver to bear the brunt of increased pressure. In tight mitral stenosis (C) where no regurgitation is possible, the left ventricle does not relieve the load of the left auricle. In fact, it becomes atrophic from the insufficient amount of blood that it has to work on. The left auricle enlarges markedly, often 5 or 6 times its normal size. The pressure in the left auricle is tremendous, but cannot be adequately relieved by the lungs because of the numerous infarcts and thrombi forming in them. The lungs, instead of being elastic enough to transmit some of the pressure back to the right heart, must bear the brunt of the pressure itself, and become voluminous. This helps explain why the death in tight mitral stenosis is essentially a pulmonary one—and why once decompensated these cases offer no mechanism of recompensation.

We thus see that the patient with pure mitral stenosis does not do as well from the start as the average case of mitral stenosis with insufficiency. He is constantly troubled by "heavy chest colds," dyspnea on slight exertion, cough and blood spitting. The pulmon-

ary symptoms are usually so prominent that he is mistakenly believed to be suffering from bronchiolitis, chronic emphysema or even pulmonary tuberculosis. Occasionally the cardiac murmur cannot be heard at all, and only the pulmonary findings suggest the condition, as in the case of tight mitral stenosis reported by us several years ago which was clinically "silent."⁶

Though the patient with pure mitral stenosis is at a disadvantage as compared to one with mitral stenosis and insufficiency (whether absolute or relative from dilatation of the *A-V* ring), the prognosis is not hopeless. If the progress of the mitral lesion is halted it may be wide enough to permit adequate circulation for many years before decompensation ensues. Even then the decompensation is not necessarily irreversible or fatal, for the mitral ostium may be still physically large enough to permit sufficient circulation of blood. If however further inflammatory calcific changes take place, and a tight mitral stenosis is formed, the symptoms of marked pulmonary stasis become rapidly aggravated, and progressive irreversible decompensation sets in, often with pulmonary embolization, bloody expectoration, pulmonary edema, and terminal bronchopneumonia. The patient may still live a while longer, the burden on the lungs being somewhat relieved by the occurrence of right heart failure with relative tricuspid insufficiency and engorgement of the liver. The relief is only temporary, however, for the lungs have been permanently damaged by diffuse infarction, fibrosis, and secondary inflammatory changes.

The diagnosis of tight mitral stenosis, then, is made on the history of persistent cardiac and respiratory discomfort which does not permit the patient at any time to be fully compensated; the prominence of cardiac and pulmonary symptoms with scanty physical signs; and the rapidity and irreversible nature of the first true decompensation, which is also the last. In its clinical essence, the damage is mechanical more than inflammatory.

If the above picture and the possibility of the existence of the condition in any case of mitral disease which fails to react to treatment is kept in mind, the diagnosis will be seldom missed. There are very few conditions which simulate the profound decompensation of these cases toward the end. Pancarditis in a younger individual may occasionally appear like tight mitral stenosis, but in pancarditis the condition is essentially inflammatory, the sedimentation rate is increased, and signs of rheumatic activity are present. In tight mitral stenosis the decompensation is purely mechanical, being due to the block at the mitral orifice.

There is no way of ascertaining, unfortunately, which cases of pure mitral stenosis will later develop into tight mitral stenosis and which will not. However, any case of this kind showing persistent symptoms not noticeably relieved by the usual treatment (digitalis, bed rest) is probably already beginning to suffer fatal changes.



FIG. 2.—Early mitral configuration, simulating an egg standing almost on its end, showing a loss of the contours of the left border, prominent pulmonary shadow and enlarged right ventricle.

The dire consequences of the first decompensation in tight mitral stenosis emphasize the importance of reducing the activities of these patients. Although caution cannot prevent the further changes in the stenosed valve caused by reinfection, it can at least keep the patient from decompensating before the fatal narrowing occurs.

Conclusions. Tight (non-regurgitant) mitral stenosis is a definite clinical as well as pathologic entity. It is a fairly common terminal stage of pure mitral stenosis, *i. e.*, a stenosis without accompanying insufficiency.

The early stage is characterized by persistent symptoms of respiratory discomfort and pulmonary stasis—cough, dyspnea and acrocyanosis. There are only moderate signs of mitral discase—a short presystolic murmur, a click of the first sound, or a marked accentuation of the pulmonic second sound—so that these cases are often mistaken for primary pulmonary affections. The Roentgen configuration appears early and is typical of pure mitral stenosis. Due to sclerotic changes in the pulmonary artery the electrocardiogram often shows high bifid *P* waves.

The later stages of the disease are caused by inflammatory changes in the mitral valve with superimposed deposition of lime, which narrow the ostium still further, making it incompatible with life. Clinically this is marked by rapidly progressive, irreversible decompensation. The most prominent symptoms are pulmonary—persistent dyspnea and blood spitting. Often a bronchopneumonia complicates the terminal picture.

It is of both diagnostic and prognostic importance to differentiate this fatal type of mitral stenosis from the more benign form of double mitral disease (stenosis with insufficiency).

We are deeply indebted to Dr. A. A. Epstein and Dr. M. A. Rothschild who kindly allowed us to study and report 6 of the cases which were on their respective medical services, and to Dr. A. Plaut for his complete pathologic studies and helpful suggestions in these cases.

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ACTIVE VERSUS CONSERVATIVE MANAGEMENT OF PLANNED DELIVERIES.

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THIS report is a survey of contrasting methods and results of parturition in 3 maternity wards during identical periods of time in Philadelphia. Statistics of births from 1931 through 1934 are presented for the purpose of comparison with the tabulations of the Philadelphia Maternal Health Committee for these years, and because of definite change in recent obstetric practice featured by forceps control, episiotomy, labor analgesia, low Cesarian section, and a new conception of eclampsia. The material for consideration is the outcome of 5000 planned deliveries in the maternity wards of the Hospital of the University of Pennsylvania, the Methodist Episcopal Hospital, and the Preston Retreat of Philadelphia, to which is added a summary of 1500 private planned deliveries from a longer period of years.

Such comparisons might be misconstrued, but when offered by the same staff member from each service should be acceptable, particularly since this type of report is rarely available by reason of the fact that few annual hospital analyses segregate the results of planned from emergency deliveries. For example, prior to this review, in our obstetrical department, results of material from the receiving ward, consulting physicians, student outside service, and prenatal clinic have been hitherto grouped together in a general summary. Therefore it is timely to know the obstetric expectations of underprivileged mothers who have registered before and delivered after the 28th week of gestation in well-appointed maternity hospitals, following adequate prenatal care.

University of Pennsylvania Maternity.* This service received a large proportion of non-pay, many part-pay and some full-pay patients, including 33.8% colored women, most of whom were discharged 12 days after delivery. Under the late Professor Piper, there were 3 interns, 1 resident in obstetrics, 3 assistants (one at a time for 2 months), and myself as alternate obstetrician. Some of the material was used in the regular semiweekly teaching clinics, but most of these deliveries were witnessed, but not examined internally, by 1 or 2 students.

Causes of Maternal Deaths. 1, Postpartum hemorrhage after breech birth and tamponade of uterus; 2, postpartum hemorrhage after mid forceps; 3, postpartum hemorrhage after version; 4, post-

partum hemorrhage after twin birth; 5, septicemia, peritonitis after twin birth; 6, septicemia, peritonitis after high forceps; 7, septicemia, peritonitis after section for ectopic gestation; 8, septicemia, peritonitis; 9, myocardial failure; 10, nephritic toxemia after Cesarian section; 11, "labor pains"—shock during labor; 12, acute dilatation of heart after spontaneous delivery; 13, "collapse" after version.

* TABLE 1.—RESULTS OF PLANNED DELIVERIES.
Over 28 Weeks Gestation.

Description.	Univ. of Pennsylvania Maternity.	Methodist Hospital.	Preston Retreat.	Personal.
Total deliveries	2157	1070	2066	1472
Total operative interference . . .	887—41.8%	169—15.8%	174—8.4%	823—56%
(Spontaneous)	1270—58.6%	901—84.2%	1892—91.6%	648—44%
Forceps	707—32.7%	118—11%	52—2.5%	636—43.4%
High-	3	3	0	20
Mid-	190	27	13	52
Low-	514	88	39	565*
Breech	61—2.8%	25—2.3%	91—4.4%	30—2%
"Spontaneous"	29	15	84	17
Extraction (decomposition)	4	1	1	13
A. C. H. forceps	29	9	6	22
Podalic version	42—2%	7—0.6%	16—0.8%	79—5.3%†
Cesarian section	76—3.5%	19—1.8%	15—0.7%	78—5.3%
Other complications:				
Surgical inductions	18	8	4	79—5.3%
Placenta previa	0	4	9	10
Complete lacerations	1	5	5	?
Eclampsia (no deaths)	6	3	7	3
Total morbidity	369—17%	114—10.6%	178—8.6%	7.9% (incomplete)
Spontaneous deliveries	11.1%			
High forceps	0			
Mid forceps	31.5%			
Low forceps	17.2%			
Maternal deaths (see causes)	13—0.6%	2—0.19%	3—0.14%	3—0.2%
Infant deaths (no corrections)	88—4.0%	30—2.8%	49—2.3%	37—2.6%
Stillborn	2.8%	1.4%	
Neonatal deaths	1.2%	0.9%	

* Mostly control.

† Including decomposition of 14 twins.

Comment. The forceps incidence is high but represents chiefly forceps control applied with the "head on the perineum" or scalp showing, inherited through a custom of 40 years from the Emeritus Professor of Obstetrics, B. C. Hirst. The total operative interference in 1934 for planned deliveries was only 14.5% lower than for the total average of 47.7% for all types of births during the previous 3-year period; but our 4-year maternal mortality of 0.6% is less than one-half that of 1.64% for the previous 3-year general rate reported by the Philadelphia Maternal Mortality Committee.

The University morbidity figures argue strongly for spontaneous delivery, in spite of absence of fever in the few cases of high forceps, which latter were performed by staff members.

No deductions or corrections are given under stillborn and neo-

natal deaths, in spite of the fact that the University Maternity syphilis frequency averages about 6%, and several monstrosities were included in this group. Forceps control should reduce infant death rate, but apparently failed to do so in comparison with the two other services, even though Foregger and Flagg apparatuses for insufflation of 10% CO₂ in 90% oxygen, and a respirator were available.

Analgesia may have accounted for some of the fetal deaths, since morphin and scopolamin or Gwathmey's rectal ether were utilized in the majority of labors, with nitrous oxid-oxygen anesthesia at delivery.

In normal as well as operative births, the management of the third stage of labor is a great source of morbidity or even mortality. In 4 of the University maternal deaths due to postpartum hemorrhage, and 3 due to sepsis, mismanagement of the placental delivery was a factor. It is possible that the plan of routine medication, namely, Ernutin mil. 0.5 intramuscularly at delivery of the infant, and Pitocin mil. 0.5 hypodermatically at delivery of the placenta, might have been related to the occurrence of postpartum hemorrhage; but it is certain that ceaseless simple holding-down of the fundus (particularly following deep etherization as for podalic version) until return of good after-contractions before expression of the placenta is vital.

Methodist Episcopal Hospital Maternity.* During the first 3 years of this survey all of the patients were obliged to pay in advance \$36 for 10 days, and during 1934, \$25, so that this material approximates that of a private ward, with no colored women, and a frequency of syphilis between 2 and 3%. The system is ideal for a small service which now averages 400 births yearly, since the deliveries are divided under a chief obstetrician between 2 continuous service associate obstetricians, with a 6-week intern supported by the chief resident physician. This management permits direct supervision by one of the staff of all operative deliveries other than outlet forceps, and all breeches and primiparas, leaving the instruction of the intern in episiotomy, outlet forceps and routine matters to the chief resident. Moreover, when the intern enters the service, he receives a condensed ward technique of 5 pages, a "code" of instructions, and has access to a large loose-leaf detailed technique book.

Causes of Maternal Deaths. 1, Pneumococcic cerebrospinal meningitis at 36 weeks gestation, contracted prior to Cesarean section performed during coma to protect the child, which survived; 2, hemorrhage and peritonitis following Cesarean section performed after 19½ hours' trial labor for contracted pelvis.

Comment. Again the forceps deliveries were mainly of the control type, and not too frequent. Cesarean sections were not too high,

and versions few. The morbidity standards, identical in all 3 institutions, namely fever of 100° F., twice consecutively in any 24-hour period excluding the first 24 hours after birth, the temperature taken every 4 hours, show fair results here.

The maternal mortality rate is excellent, but the fetal rate not so good, but again no exceptions or corrections of any sort. Analgesia in labor did not appear to account for asphyxia, about one-half of the mothers having received an average of phenobarbital sodium, gr. vi, with either morphin sulphate, gr. $\frac{1}{6}$, or codein sulphate, gr. $\frac{3}{4}$, or scopolamin, gr. $\frac{1}{150}$, terminating in light ether.

The Preston Retreat.* This unique institution, privately endowed in 1837 for obstetric care only, offers free to indigent married women of good character, up to 2 weeks prenatal, and up to 4 weeks postnatal, hospitalization in a fine maternity hospital. We therefore secure good American stock, under unusual control both indoors and out.

This is one of a very few active maternity services where the chief obstetrician personally examines and estimates the obstetric capacity of each woman prior to birth; and where truly conservative obstetrics may be attained by utilizing an experienced day or night superintendent for normal births, excluding breech deliveries.

Since the results of my predecessor, Dr. Richard Norris, and acting chief physician, Dr. Calvin Hartman, were so outstanding, I elected to continue the same conservative policy, with the results given in the table, constituting a comparison of methods and attainments not available elsewhere.

Causes of Maternal Deaths. 1, Myocardial failure following Cæsarian section; 2, cerebral abscess due to septic embolism—4 weeks after practically healed incisional infection; 3, postpartum hemorrhage following breech decomposition-extraction for placenta previa in a woman who had experienced three hemorrhages, refused to inform even her husband, and delayed entering the hospital for "fear of instrumental birth."

Comment. The figures speak for themselves, and are very creditable, showing a maternal mortality incidence nearly 5 times less than the gross rate for Philadelphia. One-third of the mothers received "standard" Gwathmey rectal ether analgesia in labor, some nitrous oxid at birth. The incidence of breech births is very high (especially in view of routine reasonable effort at one external version 4 to 6 weeks before term), but showed extraordinarily good results under conservatism, each breech birth being considered as "interference."

A possible criticism is that we are neglecting to train assistants in operative obstetrics, but we are compensating for this through the courtesy of one of our consultants, Prof. W. R. Nicholson, by instructing University of Pennsylvania graduate medical students,

who are allowed to assist with repairs and occasionally to use forceps. Furthermore, in addition to the prime consideration being the welfare of the patient, is the fact that contact with a truly conservative method of treatment in itself constitutes good training.

Personal Cases.* In contrast with the ultraconservative Preston Retreat figures, the author offers the results of a series of consecutive hospital private births beyond 28 weeks' gestation over a longer period of years.

Causes of Maternal Deaths (none preventable). 1, Hemorrhage and shock after section for full term abdominal pregnancy with the placenta attached partly to intestines; baby survived; 2, embolism on 22d day after recovery from Cesarian section and post-operative cholecystitis; 3, pneumonia, contracted prior to natural term birth.

Comment. The most significant feature of these private cases is the very small proportion of mid forceps (10%) contrasted with the outlet applications, which is explained by routine deep sedation-analgesia. The great majority of our private clinical charts show no deviation from the normal, indicating that *any elevation of temperature above 99° F. constitutes morbidity; and that primary breast engorgement does not induce fever*, even though early lactation probably by allergic reaction, and of course later inflammation may produce morbidity.

Our personal maternal mortality rate is particularly significant in view of the fact that all specialists register many women with known complications; in other words, meet with a much higher proportion of obstetric hazards than occur in the general run of pregnancies, or even in women's clinics. However, let us take inspiration from two New York City clinics, where, during 1934, in the Women's Hospital, not one of 814 registered confinements proved fatal to a mother; and in the Lying-in Hospital services where, during 1934, in 4317 live births of *all types* there were only 0.17% maternal deaths.

Conclusions. 1. In general, conservative ward obstetrics is safest for mother and child; but reasonable assistance by a trained specialist yields as good results with more relief.

2. Interns should be pre-instructed in proper methods of delivery and the importance of rigid adherence to technique, and must be supervised in every abnormal labor and in all operative deliveries.

3. A member of the major obstetric staff should be present at all operative deliveries other than outlet forceps, and at all breech deliveries.

4. No effort whatever should be made to interfere with natural birth for the purpose of exhibition to students, since demonstration forceps or other operative deliveries instituted only for instruction of students or interns have been found unjustifiable.

OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

THE RELATIONSHIP OF NUTRITIONAL DEFICIENCY, HYPOPROTEINEMIA, AND ELEVATED VENOUS PRESSURE TO WATER RETENTION IN PREGNANCY.*†

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APPROXIMATELY 25% of present-day maternal mortality is due to toxemia of pregnancy. Although such disorders as the anemias and polyneuritis of pregnancy have been included under this designation, these conditions may now be considered due to nutritional deficiency.¹⁻⁵ The term toxemia of pregnancy, as employed in this paper, designates the occurrence of arterial hypertension, with or without other abnormalities, during the latter months of pregnancy, in women known to have had normal blood pressures and no albuminuria early in gestation. The term eclampsia is reserved to designate the occurrence of convulsions and coma during the latter months of pregnancy, in labor, or during the puerperium, in women not presenting evidence of epilepsy, brain tumor or other adequate cause for the condition. Many observers believe that such events are the result of the action of one or more hypothetic toxins elaborated by the maternal or fetal organism. Although albuminuria is a common concomitant of toxemia, hypertension alone occurred in 585 of the 1036 cases of toxemia reported by Tillman and Watson.⁶

When convulsions and coma occur in the latter part of pregnancy or the puerperium, albuminuria and hypertension are usually present. However, convulsions and coma, considered to be eclampsia, have been reported without albuminuria by numerous clinicians,⁷⁻¹⁰ and more rarely, have been observed in the absence of arterial hypertension.¹⁰⁻¹¹

There remains, however, one other condition which is an exceedingly common concomitant of any and all of these other manifestations of toxemia, that is edema. In fact, most observers believe that either gross or occult edema is the *sine qua non* for the diagnosis of true toxemia of pregnancy. However, Fink¹² claims that 95% of all pregnant women have some degree of occult or gross edema.

* This work was made possible through the coöperation of the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, to whom the writer acknowledges his indebtedness.

† This paper was presented before the American Society for Clinical Investigation at Atlantic City, N. J., May 6, 1935.

More than 60 years ago, Rosenstein¹³ advanced the thesis that cerebral edema was the cause of eclampsia. This he regarded as due to the effusion of serum from the "too-watery" blood into the cerebral tissues. Charpentier,⁸ 13 years later, agreed with several compatriots that a diminished amount of albumin in the blood was a predisposing cause in the production of eclampsia.

More recently Wieloch¹⁴ has observed the universal occurrence of water retention in his cases of toxemia of pregnancy, and Zangemeister¹⁵ has actually demonstrated edema of the brain by means of trephining the skulls of eclamptic patients. Prutz,¹⁶ and Arnold and Fay,¹⁷ among many others, have made similar observations postmortem. Bingham¹⁸ showed that toxemia developed only in those women who gained weight excessively. Although the cause of this weight gain was not determined, water retention might be its explanation. The cause of the marked water retention, which by general consensus of opinion¹⁹ is so uniformly present in toxemia, has been variously ascribed to an excess production of pituitary antidiuretic hormone,²⁰ to primary kidney disease,²¹ to a disturbance in the stability of the plasma colloids,²² and to pressure of the enlarged uterus on the ureters,²³ among many other hypothetic causes. However, no satisfactory evidence has been presented for any of these theories. No modern investigator has reexamined the hypothesis of Rosenstein, Prodhomme and others in the light of present-day knowledge concerning the mechanism of edema formation. Our understanding of this mechanism begins particularly with Starling's²⁴ demonstration of the rôle which the colloid osmotic pressure of the plasma proteins plays in counter-balancing the mechanical effect of the intra-capillary blood pressure. From Peters and Van Slyke's²⁵ excellent summary we learn that three main factors are involved: the intra-capillary blood pressure, the osmotic pressure of the plasma proteins, and the capillary permeability. In addition, edema apparently may occur as a result of the lack of certain still unknown accessory food factors (Yang and Huang,²⁶ Youmans,²⁷ Elsom²⁸ and others). Furthermore, Weech *et al.*²⁹ have recently shown that edema is formed in poorly nourished dogs at a much higher level of plasma proteins than in well-nourished dogs whose plasma proteins have been depleted by plasmapheresis. It is also apparent that edema cannot be formed unless there be supplied to the organism the necessary materials, that is, water and salt.

It is pertinent to consider at this point what changes occur in these various factors involved in water exchange during normal pregnancy. Grzechowiak³⁰ and Mufson³¹ have directly measured the intracapillary pressure in pregnancy. Although it is not elevated in normal pregnancy, they found it to be markedly so in eclampsia and many cases of toxemia. However, the work of Landis and Gibbon³² has so clearly demonstrated that the filtration of fluids out of the capillaries is directly proportional to the venous

pressure that studies of the latter in pregnancy by Runge³³ are important. The maximum venous pressures which he observed in normal non-pregnant subjects were 6.6 cm. and 7.2 cm. of water in the arm and leg respectively, contrasted to 8.9 cm. and 8.8 cm. respectively in normal women during the first 7 months of pregnancy and 9.8 cm. and 31.4 cm. respectively in normal women in the last 2 months of pregnancy. Barath and Weiner³⁴ found venous pressures of from 10 to 18 cm. of water in the arm at the end of normal pregnancy. It is thus apparent that normal pregnancy, particularly in the later months, may result in a distinct elevation of the venous pressure. If this is due to the mechanical effect of the enlarged uterus, one might expect it to be most marked in primiparæ with taut abdominal walls, in the obese, in the pyknic type, and in women with very large uteri from twin pregnancy or hydramnios. There is no doubt but that there is a higher incidence of toxemia in such individuals.^{35,36,37} It is also apparent that the venous pressure is tremendously raised during the active stage of labor, during which time contractions of the abdominal musculature and diaphragm result in expulsive efforts.³⁸ It may be significant that 53% of all reported cases of eclampsia summarized from every available source³⁹ occurred during labor and 21% shortly after delivery. Unless a mechanical effect is involved, it is difficult to understand why three-fourths of all cases of eclampsia should occur during this relatively short period of the gravid state.

The concentration of the plasma proteins has been regularly found lowered during pregnancy.^{22,41-44} This is corroborated by the data to follow. Eufinger,²² Plass,⁴³ Eastman⁴⁴ and others have found this lowering of the plasma protein concentration most marked in toxemias of pregnancy and particularly in eclampsia, which is also evident from the data in this paper. The albumin fraction which has 4 times the osmotic pressure of the globulin fraction is particularly reduced. Although the degree of reduction of the osmotic pressure of the plasma proteins in pregnancy is ordinarily not below the so-called critical level for edema formation in the normal individual, it should be remembered that, in the presence of a second disturbance affecting filtration, there may be a much higher critical level, as has recently been shown in heart disease by Thomson.⁴⁵

The cause of the lowering of the plasma protein concentration in pregnancy has not been clearly defined. One cause is apparent. It is recognized that the fetus draws upon the maternal organism for dietary factors, including its protein precursors, no matter what depletion of the mother results.¹ Therefore, if the mother's protein intake has been barely sufficient for her own economy and no change is made in her diet after pregnancy occurs, depletion of the mother's protein, especially in the last trimester of pregnancy, may be inevitable.

Disturbed gastro-intestinal function can condition dietary deficiencies. Such disturbances are common in pregnancy^{2,46,47} and could play a rôle in conditioning protein deficiency in certain pregnant women in spite of an apparently adequate diet. Definite evidence on this point is, however, lacking. The part played in pregnancy by a failure to manufacture proteins through a disturbance of the organs involved in their production is entirely hypothetical but possibly important.

Observations. *The Plasma Proteins in Normal Pregnancy and in Toxemia.* The concentration of the total plasma protein and of the plasma albumin was determined by a modification of the method of Howe⁴⁸ on oxalated venous blood drawn without stasis, after the subject had been recumbent for at least 15 minutes. These observations were made on blood from the antecubital veins of 65 pregnant women. Of these 35 were normal and in the last 2 months of pregnancy, 20 were suffering from toxemia during a similar period of pregnancy, and 10 had eclampsia. The 20 with toxemia were known to have had normal arterial blood pressures and no albuminuria early in pregnancy, although at least 3 had had toxemia in preceding pregnancies, 1 having had eclampsia twice. At the time that blood was withdrawn for these determinations, each of the 20 patients with non-convulsive toxemia had a blood pressure of 150 (systolic) and 100 (diastolic) or higher. Seven had from 0.2 to 2 gm. of albumin per liter of urine (Tsuchiya method). The remaining 13 had only very slight traces of albumin in the urine. Only 3 had gross edema.

Each of the 35 normal pregnant women was closely questioned as to her usual protein intake both during and prior to pregnancy. Before any chemical analysis was made of the plasma, each dietary history was evaluated as either average or low in protein content. Of these women 20 had had diets containing moderate amounts of protein (estimated at 60 to 100 gm. per day), and 15 had had definitely low protein diets (estimated at less than 60 gm. per day). The failure to encounter any women with high protein intakes can probably be explained by the fact that they were all clinic patients and hence unable to afford the more costly protein foods in large amounts.

In Chart I are presented the plasma albumin concentrations of the 65 women grouped according to the condition which they presented.

It is apparent that in toxemia, with or without convulsions, the plasma albumin concentration is decidedly lower than in normal pregnant women. The average concentration of the plasma albumin in the 10 patients with eclampsia was 2.6%, in the 20 patients with toxemia without convulsions 3.1% and in the 35 normal pregnant women 3.56%. The lowering of the plasma albumin concentration in the 20 patients with non-convulsive toxemia can hardly be

ascribed to a loss of albumin in the urine, as 13 of these women had only very slight albuminuria. The average concentration of plasma albumin was lower in the normal subjects with poor protein intakes than in those with average intakes.

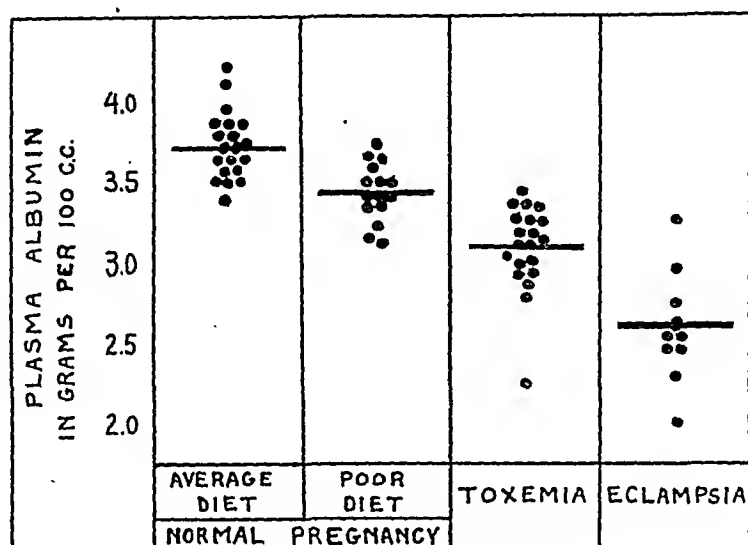


CHART I.—Plasma albumin concentration during the last 2 months of gestation in 20 normal women on average protein diets, in 15 normal women with low-protein intakes, in 20 women with non-convulsive toxemia of pregnancy, and in 10 with eclampsia. Each dot represents 1 patient. The horizontal lines represent the average values for each group.

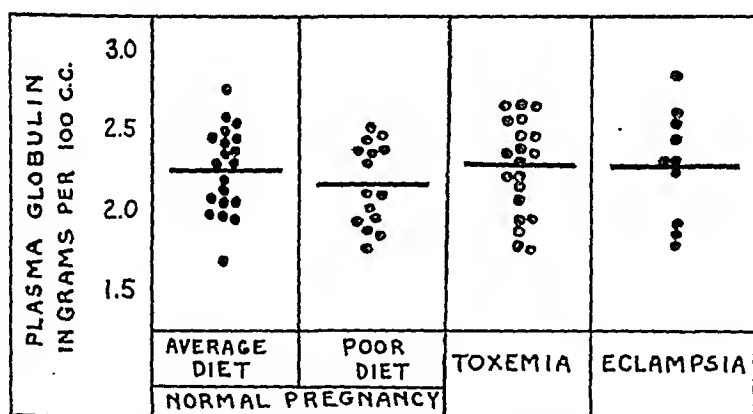


CHART II.—Plasma globulin concentration in the same group as in Chart I.

In Chart II the data on plasma globulin concentration obtained on the same 65 women is shown. The entire absence of correlation between diet, toxemia or eclampsia and the level of globulin is obvious.

Because, however, it is the colloid osmotic pressure exerted by both the albumin and globulin that is of importance with regard to

edema formation, the osmotic pressure of both fractions together has been calculated by Wells, Youmans and Miller's method⁴⁹ in each case (Chart III). The average osmotic pressure was lowest in eclampsia (175 mm. of water), next in non-convulsive toxemia (215 mm.), next in normal pregnant women with poor diets (232 mm.), and highest in those with good diets (258 mm.).

The Venous Pressure in Normal Pregnancy and in Toxemia. The venous pressure of 20 pregnant women during the last trimester of pregnancy, whose arterial blood pressures were 150 mm. Hg systolic and 100 mm. Hg diastolic or higher, and of 20 normal pregnant women during the last 2 months of gestation was determined by

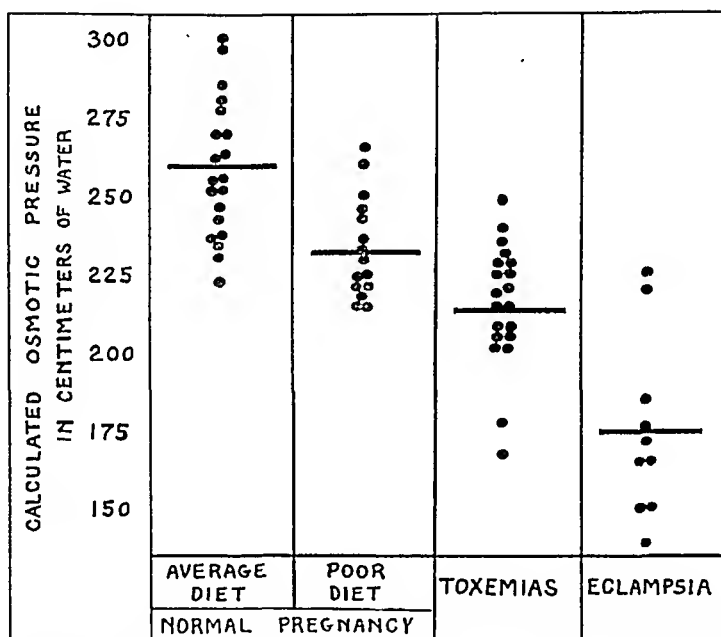


CHART III.—Calculated osmotic pressure of the total plasma proteins in the same group as in Chart I.

the method of Moritz and Tabora.⁵⁰ Readings were made after the subjects had been in a recumbent position for at least 15 minutes. The average venous pressure of normal non-pregnant individuals has been given by Eyster⁵¹ as 5 cm. of water, with a maximum of 11 cm. During the last 2 months of normal pregnancy (Chart IV) the average venous pressure of 20 women was 10 cm. of water with a maximum of 18 cm. The average venous pressure of the 20 patients with toxemia was 13.3 cm. of water, a value not significantly different from normal pregnant women but distinctly higher than in normal non-pregnant subjects.

The impression obtained was that the venous pressure was particularly elevated in the short, stocky, obese women and in the

extremely thin and rather frail appearing women whose abdomens seemed hardly large enough to accommodate a full-term pregnant uterus.

Dietary Histories of Women with Toxemia of Pregnancy. The dietary histories of 20 pregnant women with toxemia, were carefully studied. Six of these women had had severe nausea and vomiting for several months early in pregnancy which had greatly limited their total intake, concentrated carbohydrates being their chief food during the period of emesis. Two other patients had had

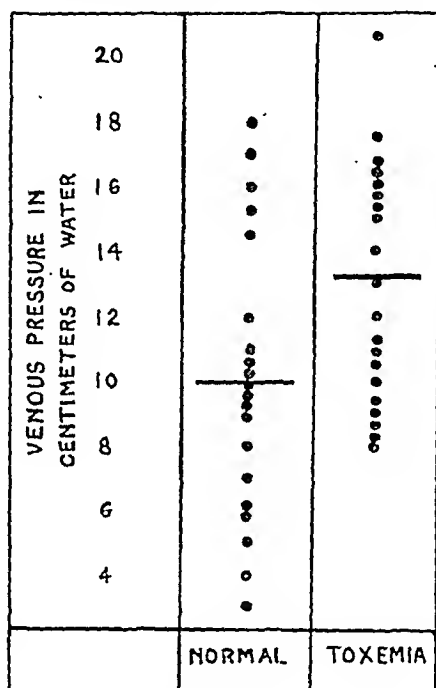


CHART IV.—Venous pressures in 20 normal pregnant women and in 20 with non-convulsive toxemia of pregnancy, all within the last 2 months of gestation. Dots and horizontal lines as before.

moderate emesis which had caused them to restrict their food to a certain extent. Of the 20 women, 18 had eaten little meat or other protein foods, not only during pregnancy but often over a period of years. The daily protein intake of these patients was estimated at less than 50 gm. daily. At least half of them stated that they were "poor meat eaters." Of the 20, 9 specified that they were very fond of and ate sweets and pastries in large amounts. Fifteen, who had accurate knowledge of their weight before pregnancy, had gained 20 to 44 pounds during gestation.

Results of Treatment of Toxemia of Pregnancy with a Special Diet High in Protein. Of the 20 pregnant women with toxemia, each of whom had an arterial blood pressure of 150 (systolic) and 100 (diastolic) or higher, 15 were given a diet containing 260 gm. of protein, 150 gm. of carbohydrate and 70 gm. of fat (2270 calories).

The protein was supplied in the form of lean meats, egg whites, skimmed milk and 300 gm. of raw liver pulp daily. Fluids were allowed freely. No purgation was employed. These patients were in the hospital during the period of observation but were not confined to bed. Ten of these 15 also received by daily intramuscular injections 5 cc. of a vitamin B₁ concentrate and 5 cc. of Solution Liver Extract—Lilly (N. N. R.).* The latter is believed to contain the pellagra and black-tongue preventative fraction of the vitamin B complex.

The weight changes of these 15 women at the end of a fortnight of this treatment are shown in Chart V. In general, weight was

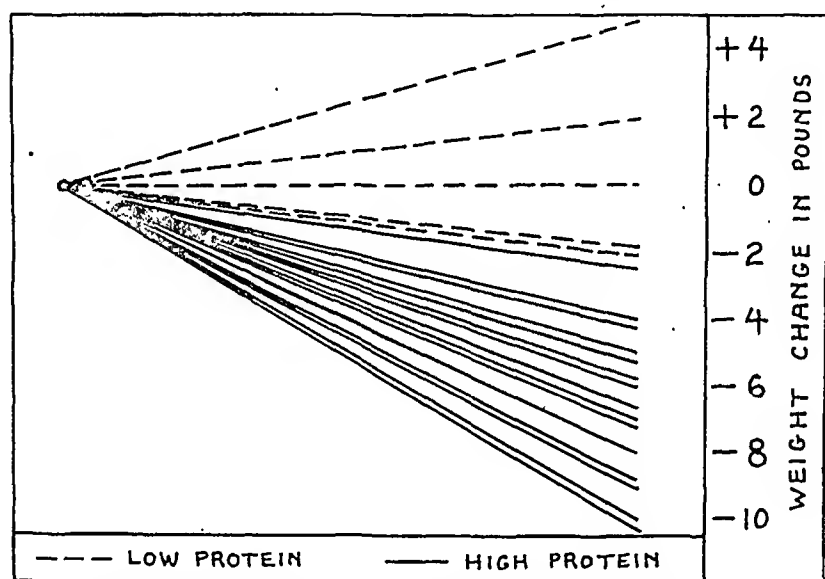


CHART V.—Weight changes after 2 weeks of 5 women with non-convulsive toxemia of pregnancy receiving a 20 gm. protein diet and of 15 similar women receiving a 260 gm. protein diet and parenteral injections of vitamin B.

lost steadily during this period in spite of the fact that they had daily about 2270 calories and were largely at rest. The amount of weight lost depended particularly on the proportional amount gained during the earlier months of pregnancy. In 3 patients gross edema completely disappeared, so that there was a marked loss in weight within 20 days. After the period of weight loss or within 3 weeks or less, the patients usually showed slow gains in weight consistent with the caloric intake. Rarely did the weight reach a level as high as that observed upon admission to the hospital. That this loss of weight during the first 2 or 3 weeks of treatment was due to the disappearance of either gross or occult edema seems to be very probable.

* Kindly supplied by Eli Lilly and Co., Indianapolis, Ind.

Coincident with the loss of weight, symptoms such as headache and visual disturbances were abated. In Chart VI, the arterial blood pressure of these women is shown at weekly intervals. In no case did the pressure rise after treatment was instituted. It is of interest that in every case the arterial blood pressure fell to below a systolic level of 140 mm. of mercury and to below a diastolic level of 90 mm. of mercury within 3 weeks of commencing treatment. The records indicate that the more acute the onset of the arterial

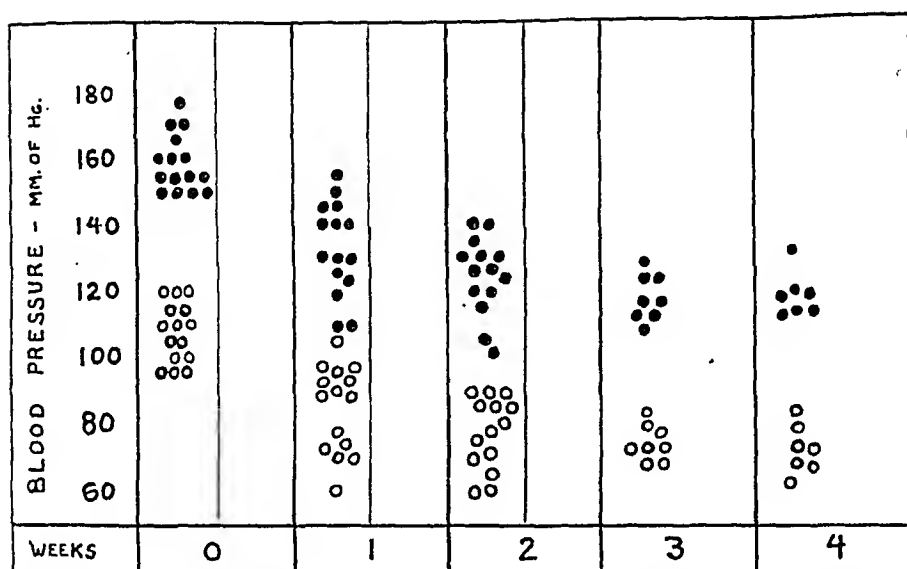


CHART VI.—Arterial blood pressures in successive weeks of 15 women with non-convulsive toxemia of pregnancy receiving a high-protein diet. The solid circles represent the systolic blood pressure, the open circles, the diastolic blood pressure. Seven of the patients were delivered by the end of the third week. No postpartum pressures are shown.

hypertension and the earlier the treatment, the more rapid was the response.

Albuminuria either remained unchanged or decreased in degree. No evidence suggesting that such a diet might lead to uremia can be drawn from Table 1, in which are presented the non-protein nitrogen values for these 15 women before and after the institution of the high-protein diet.

The calculated osmotic pressure of the plasma proteins in these women rose in 2 weeks an average of 7% of the initial level, usually by virtue of rises in both albumin and globulin fractions.

No fetal mortality occurred after the institution of this special diet.

After 3 of the above patients received the special diet in the hospital for 1 month, they returned to their homes, continuing the diet to the best of their abilities, during a period of 1 to 2 months

TABLE 1.—THE NON-PROTEIN NITROGEN OF THE BLOOD PLASMA IN 15 PATIENTS WITH NON-CONVULSIVE TOXEMIA OF PREGNANCY BEFORE AND AFTER ADMINISTRATION OF A HIGH-PROTEIN DIET.

Before mg. per 100 cc.	After mg. per 100 cc.
15	25
20	27
18	25
18	30
18	33
22	32
13	35
17	25
15	27
18	23
18	31
13	25
14	28
16	27
11	22
Average 16.4	Average 27.6

before each was delivered. In no instance was there any return of toxemic symptoms. Weight curves showed no evidence of recurrence of occult edema.

Results of Treatment of Toxemia of Pregnancy with a Low-protein Diet. Five of the 20 pregnant women with toxemia, with as nearly as possible identical signs and symptoms as the 15 women mentioned immediately above, were given a diet containing 20 gm. of protein, 65 gm. of fat and 400 gm. of carbohydrate. This diet contained 2265 calories or approximately the same number as the high-protein diet. However, it contained no meat, milk, fish, or eggs. The sodium chlorid content was essentially the same as that of the high-protein diet. The vitamin content was low. Fluids were allowed freely and no purgation was employed. The weights of these 5 women during a period of 2 weeks are shown in Chart V. One patient gained 5.25 pounds, a second 1.75 pounds, and the remaining 3 lost 0.25, 1.75 and 2 pounds each. The blood pressure (Chart VII) in 2 cases had fallen to normal within 2 weeks, in the remaining 3 patients it either rose or was stationary. Albuminuria was unchanged in 3 of the 5 patients, and increased from a faint trace to 0.3 and 15 gm. per liter respectively in the remaining 2 women. The calculated osmotic pressure of the plasma proteins fell an average of 9% of the initial value in these 5 women, the loss being chiefly at the expense of the albumin fraction.

Discussion. It is apparent that edema disease in pregnancy, mechanically complicated as it is by the large intraabdominal mass of the pregnant uterus, an elevated venous pressure, and the constant drain on the protein reserves of the mother, must necessarily differ from edema disease in the non-pregnant individual. It is of

interest, however, that Yang and Huang²⁶ have recorded the occurrence of convulsions as well as arterial hypertension in the "wet" form of beriberi. Cowgill and his associates⁵² have shown that the need for vitamin B increases with elevation of the metabolism. Since the basal metabolic rate is raised about 20% in pregnancy, considerably more vitamin B is probably required by pregnant women. Hence a deficiency of this factor may easily occur in pregnancy.

There is evidence to suggest that hemoglobin regeneration following the administration of iron is slower in pregnant than in non-pregnant patients with hypochromic anemia.¹ One would expect

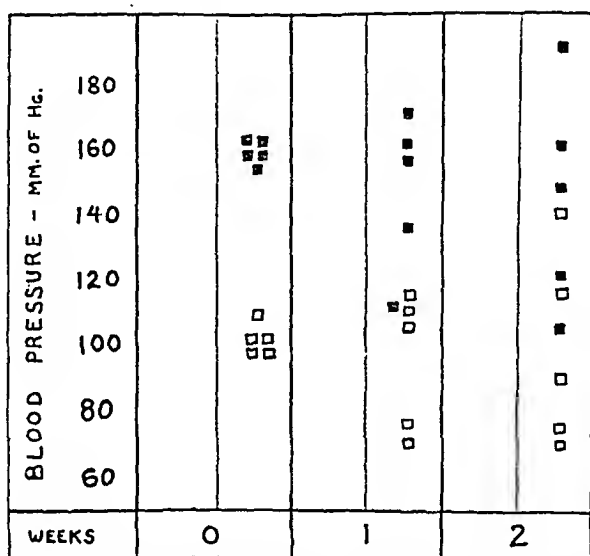


CHART VII.—Arterial blood pressures in successive weeks of 5 women with non-convulsive toxemia of pregnancy receiving a low-protein diet. The solid squares represent the systolic blood pressure, the open squares, the diastolic blood pressure.

similarly that regeneration of plasma protein would be slower in pregnant women because of the constant demands of the fetus.

The weight changes of the 15 patients receiving the high-protein diet may be ascribed to any number of factors, such as rest in the hospital, or an increased nitrogen excretion resulting in diuresis. However, the failure of the control group to show changes of a similar magnitude suggests that the rest obtained is but a minor factor. Whether the patients who received the high-protein diet and injections benefited because of the protein content of the diet or because of receiving accessory food factors or both, cannot be determined at present.

The rôle of tissue resistance, lymph flow, and capillary permeability in edema formation in pregnancy has not been touched upon because of the paucity of our knowledge of these factors. The one

pertinent study⁵³ which has been made of edema fluid in toxemias of pregnancy has shown its protein content to be low, suggesting that there is no abnormal alteration of capillary permeability such as exists in certain other types of edema.

Because the arterial blood pressure is subject to spontaneous fluctuations both in normal and hypertensive subjects, and because rest frequently lowers both systolic and diastolic levels, no conclusions should be drawn from the fact that there was a lowering of the arterial blood pressure in each of the 15 women treated with the high-protein diet. It should be noted that this also occurred in 2 of the 5 patients receiving the low-protein diet.

The observations recorded in this paper fail to substantiate the prevalent belief that patients with toxemia of pregnancy should be treated by means of a restricted protein intake. It must be remembered, however, that none of these patients had either albuminuria or arterial hypertension during the first half of pregnancy. Approximately 5 of every 6 patients diagnosed as having toxemia of pregnancy in our pre-natal clinic were excluded from this study because there was no satisfactory evidence that the blood pressure was normal and the urine free of albumin during the early months of pregnancy. It might be added that a few observations, not recorded here, fail to show that any harm results from the use of high-protein diets in pregnant women with pre-existing arterial hypertension or albuminuria, or does such a diet appear to have any beneficial effect on such women.

Summary. 1. In 20 cases of non-convulsive toxemia of pregnancy the average osmotic pressure of the plasma proteins was 215 mm. of water, in 10 cases of eclampsia it was 175 mm. of water and in 20 normal pregnant women with adequate diets it was 258 mm. of water. In 15 normal pregnant women who had partaken of diets low in protein the average osmotic pressure of the plasma proteins was 232 mm. of water.

2. The average venous pressure in 20 normal pregnant women during the last 2 months of pregnancy was 10 cm. of water (range 3 to 18 cm.) and in 20 patients with non-convulsive toxemia of pregnancy 13.3 cm. (range 8 to 20.5 cm.), values which are at least twice as high as average figures for normal non-pregnant subjects.

3. The dietary histories of 20 toxemic pregnant women showed a low-protein intake, probably less than 50 gm. per day, frequently over a period of years.

4. Fifteen women suffering from toxemia of pregnancy were treated by means of a diet containing 260 gm. of protein, 150 gm. of carbohydrate and 70 gm. of fat. Ten also received parenteral injections of a vitamin B₁ concentrate and Solution Liver Extract—Lilly (N.N.R.), the latter because of its content of the pellagra-preventative portion of the vitamin B complex. Each of the 15 women showed a loss of weight readily attributable to decrease of

occult or gross edema, together with a gradual disappearance of the signs and symptoms of toxemia. No fetal mortality occurred after treatment had been instituted.

5. Five similar pregnant women suffering from toxemia were treated by means of a diet of approximately equal caloric value containing 20 gm. of protein, 400 gm. of carbohydrate, and 65 gm. of fat. No significant loss of gross or occult edema occurred. Two of the patients became decidedly worse during a period of 2 weeks.

6. It is believed that a manifestation of toxemia of pregnancy is water retention. This water retention probably occurs as a result, among other factors, of a lowered osmotic pressure of the plasma proteins, usually in the presence of an increased venous pressure. The results recorded in this paper suggest that a restricted dietary intake of protein in pregnancy is harmful, and that no injurious consequences follow the administration of high-protein diets to women with toxemia of pregnancy. The beneficial results observed in these patients may well have been due to the large protein intake and to the parenteral administration of accessory nutritional factors.

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(Titles have been omitted for sake of brevity).

ERYTHEMA ANNULARE RHEUMATICUM.

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In 1922 Lehdorff and Leiner,¹ under the title "Erythema Annulare" published an account of a typical exanthem occurring during the course of rheumatic endocarditis. Lehdorff,² in 1930, again described "Erythema Annulare Rheumaticum" and emphasized the fact that it occurs only in rheumatic children with endocardial involvement. While making the rounds at the Mautner-Markhof Kinderspital in Vienna in 1925, the late Professor Leiner demonstrated this rash to me in a child with rheumatic endocarditis. Since then I have had the opportunity of following a group of children suffering with rheumatic endocarditis at the Spaulding School for Crippled Children, and during the course of my examinations I have noted this distinctive rash in 6 children. The following cases may be cited:

Case Abstracts. CASE 1.—T. J., a 14-year-old boy, had frequent attacks of tonsillitis. After an attack of scarlet fever at the age of 7 years, he developed an arthritis which was followed by mitral endocarditis. Two sisters have had rheumatic fever and rheumatic endocarditis. At the time of examination for admission to the Spaulding School, November 6, 1931, it was stated that he had had frequent attacks of epistaxis for a year, and that the eruption appeared frequently on his chest, abdomen and back, especially when he did not feel well. The patient had been followed at the Illinois Research Hospital by Dr. Gustav Weinfeld and was referred by him to the Spaulding School. The child was fairly well developed, skin was somewhat pale, tonsils had been removed, throat was clear, heart showed moderate enlargement to the left, there was no diffusion of the apex, and no precordial bulge. There was no thrill. A presystolic, systolic murmur, best heard at the apex, was transmitted to the axilla and to the base. Pulmonary second sound was accentuated, and the aortic second sound was clear. There was no clubbing of the finger nails. An annular erythema, consisting of narrow rings 1 to 1.5 cm. in diameter, of a pale pink color, was noted on the chest, abdomen, and to some extent on the back. The rash was of a macular character and the skin was free from edema, hemorrhage, or itching. The patient was unaware of the rash, except when he looked at his skin and noted its occurrence. On questioning the mother and the boy, the fact was brought out that whenever he did not feel up to standard or had a cold with fever, the rash occurred more prominently and lasted for some days. On Roentgen ray examination, a teleoroentgenogram at 6 feet distance revealed a moderate enlargement to the left with a mitral contour of the left heart border. The electrocardiogram showed a rate of 96 with a *P-R* complex of 0.16 seconds. There was a sinus rhythm with a slurring of the *Q-R-S* complex in I, II and III. *T* III was isoelectric. There was a left axis deviation. The systolic blood pressure was 128, diastolic 70. The red blood count was 6.1 million, hemoglobin (Tallqvist) was 85%; white blood cells, 7550.

Progress at School. The boy has attended school fairly regularly and has been well with the exception of occasional upper respiratory infection. At times when he has a slight temperature elevation or a cold the school nurse reports that the annular erythema noted at the first examination reappears on his chest and abdomen. (Fig. 1.)

CASE 2.—J. D., aged 14, was referred from the Municipal Tuberculosis Dispensary, and examined for admission to the Spaulding School January 3, 1933. At 10 the patient had an attack of acute rheumatic fever with elevation of temperature and swollen and painful joints of the shoulders, hands, knees and ankles. Subsequent to this attack the child was examined by a physician and the mother was told that he had heart disease. A similar attack of rheumatic fever was experienced in October, 1932, though of a shorter duration. The child had had frequent attacks of tonsillitis, though there was no history of any contagious disease. Two siblings were living and well. The patient was a thin, poorly nourished boy, and rather pale. There was no cyanosis. The throat was clear, the tonsils hypertrophied and cryptic. The heart was markedly enlarged downward to the left. The apex beat was diffuse in the fifth and sixth left interspaces outside of the midclavicular line. The precordium was bulging and there was a definite heave at the back systole. There was no thrill. There was a presystolic, systolic murmur at the apex transmitted to the axilla, and a diastolic murmur over the aortic area transmitted to the third interspace to the left of the sternum. The second pulmonic sound was poorly transmitted. The heart rhythm was regular, and a Corrigan pulse was noted. At the time of the examination the child had a definite nasopharyngitis, with a temperature of 99.6° F. An annular erythema of bluish-pink color and macular

in nature was noted over the lower abdomen from the level of the umbilicus to the symphysis pubis. The rash consisted of narrow rings about 1 cm. in diameter, some of which formed circles, others were serpentine or crescentic in form.

Progress. The boy attended school irregularly until the fall of 1933 when he was taken ill with another attack of rheumatic fever. Following this he developed a decompensated heart, was hospitalized for several months and died at home in February, 1934. Autopsy could not be obtained.

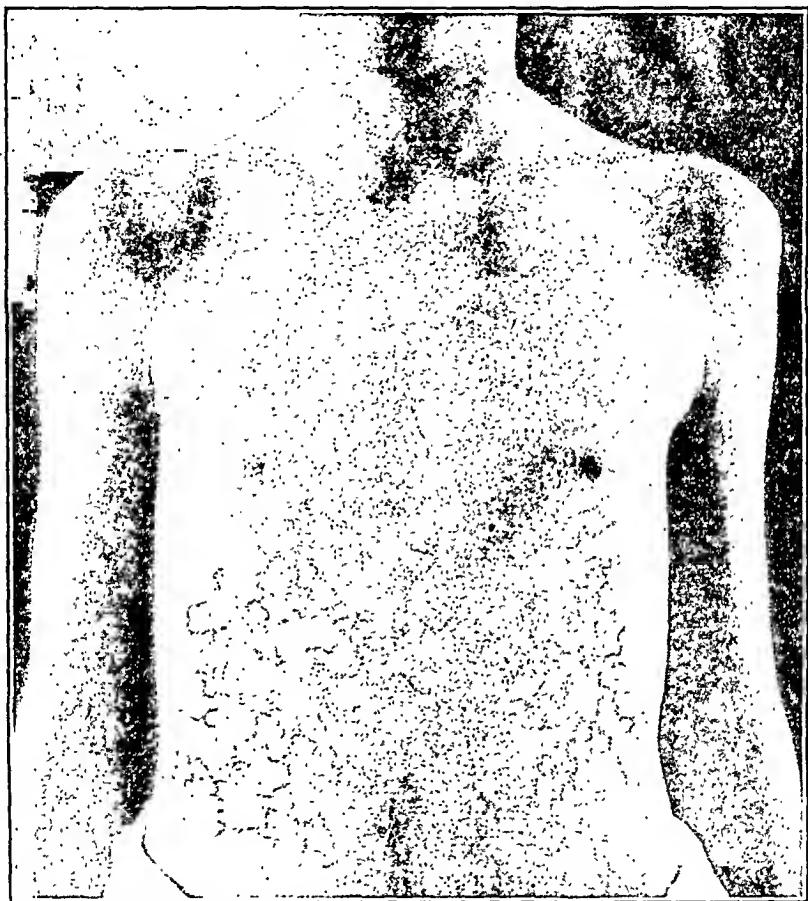


FIG. 1.—(Case 1.) Erythema annulare rheumaticum, as noted in a 14-year-old boy suffering with rheumatic endocarditis.

CASE 3.—M. H., a 12-year-old girl, was referred to the Spaulding School by the County doctor. She was examined on November 22, 1933, for admission. She had scarlet fever (1921), measles (1927), diphtheria and mumps (1929) and whooping cough (1930); also occasional attacks of tonsillitis. In December, 1930, she had an attack of rheumatic fever, at which time she was confined to bed for 2 weeks with fever and swollen joints. In April, 1931, she was seen at the Northwestern University Dispensary, complaining of joint pains. At this time she was sent to Wesley Hospital, where she was confined for 7 weeks. Two siblings are living and well. From time to time, the mother states, nodules have appeared on the

child's elbows, wrists and feet. Physical examination at the time of application for admission to the Spaulding School, showed a tall, thin, red-haired girl with a mitral facies. Her tonsils were rather large and cryptic. Her heart was somewhat enlarged to the left and the right border was at the sternal margin. The apex beat was diffuse, no thrill was noted. A presystolic, systolic murmur was heard at the apex and transmitted to the axilla. The aortic second sound was clear and the pulmonic second sound was markedly accentuated. Blood pressure was 134 systolic, 80 diastolic. There was no clubbing of the fingers and no rheumatic nodules were noted at the time of examination. At the time of this examination the skin was clear.

Progress at School. February 6, 1934, the child was reexamined because she had been out of school for 1 week with a cold. At this time an annular erythema, consisting of a macular, pink rash was noted over her thorax, made up of rings from 1 to 2 cm. in diameter. The physical examination was essentially similar to that recorded above.

CASE 4.—E. S., was admitted to the Spaulding School on September 11, 1931, aged 11 years. He had measles, scarlet fever, and diphtheria in 1924, and had been confined to the City Contagious Diseases Hospital. In 1927, he had an attack of acute rheumatic fever, following which his tonsils had been removed. He was a rather thin boy of 11, throat clear, tonsils removed. His heart was moderately enlarged to the left, the rhythm was regular, there was a systolic, presystolic murmur at the apex, transmitted to the axilla. No thrill. The aortic second sound was clear, pulmonic second sound accentuated. Red blood cells, 4,950,000; hemoglobin, 85% (Tallqvist); white blood count, 7150. The Roentgen ray teleoroentgenogram showed moderately enlarged heart with a prominence in the left auricular region, suggesting the contour of a mitral lesion. The electrocardiogram showed a rate of 96, P-R interval 0.16 with normal rhythm; Q-R-S was slurred and widened in all leads; T I diphasic and a left axis deviation.

Progress. Attended school fairly regularly, though in February and March of 1933 he was confined to his home with an attack of acute rheumatism, at which time he had fever and swollen joints. On February 16, 1934 he was examined after an absence from school because of a cold. This examination was essentially the same as that on admission, with the exception that he was quite thin and pale. There was a diffusion of the apex beat, a marked bulging and heaving of the precordium. The rhythm was regular. Slight clubbing of the finger nails was noted. No rheumatic nodules. Over the skin of the chest and back there was a diffuse annular erythematous eruption, consisting of pink macular rings 1 to 2 cm. in diameter.

CASE 5.—R. N., admitted to the Spaulding School on March 8, 1935, aged 8, complained of shortness of breath on exertion. He had an attack of acute rheumatic fever in October, 1934, following which it was noted he had heart trouble. On physical examination it was noted that the patient was a small thin boy, rather pale, the heart rate was rapid and the apex slightly outside of the midclavicular line. Presystolic, systolic murmur at the apex transmitted to the axilla, second pulmonic sound accentuated. An annular erythematous rash was noted over the lower portion of the chest and the upper part of the abdomen. The lesions were circular and macular in nature. The rings were 1 to 1½ cm. in diameter, and the skin was free from edema or hemorrhage.

CASE 6.—C. J., a 14-year-old boy, complains of shortness of breath and fainting spells; admitted to the Spaulding School on March 8, 1935. In the past year he has had so-called growing pains. Tonsillectomy in 1929; scarlet fever in 1933, and pneumonia in January, 1935, at which time his heart trouble was discovered. Rather thin, small, pale boy. Apex beat is

diffuse. There is a slight precordial bulge with a heave, no thrill, heart is enlarged to the left, out and down, with slight enlargement to the right. Presystolic, systolic murmur at the apex which is transmitted to the axilla and to the base. Pulmonic second sound accentuated, the aortic second sound is normal. An annular erythematous rash is noted on the chest and abdomen and extends around the flanks and over the lower back. Small erythematous circles are also noted in the cubital spaces and along the flexor surfaces of the forearms. The rings are macular in nature and measure from 1 to 2 cm. in diameter. The mother states that she has noticed this rash when the boy felt poorly or had a cold.

Discussion. Since the publication of the description of erythema annulare rheumaticum by Lehnndorff and Leiner (1922) it would seem of interest to examine the literature both before and after their description of this specific skin rash to note its observance by other authors. If we examine Cheadle's³ classic monograph "The Various Manifestations of the Rheumatic State" (1889) we note as a frontispiece a colored print sketched from life, depicting a posterior view of the head and back of a child, showing large subcutaneous nodules on the occipital region of the head, along the spine, over the wings of the scapulæ and over the posterior iliac crests. Besides these nodules we note annular skin lesions which in the picture appear similar to erythema annulare rheumaticum, and which Cheadle terms erythema marginatum (Fig. 2). On page 46 of this treatise, he states: "The connection of erythema exudativum with the rheumatic state appears much more clearly in the case of children than of adults. With the latter it occurs occasionally; with children, according to my experience, it is common." According to Cheadle, the skin manifestations of rheumatic fever appear in various forms, either as erythema marginatum, as erythema papulatum, as erythema nodosum, or as urticaria. The erythema marginatum, according to Cheadle, is the most common type found. The following from Cheadle agrees with the precepts of Lehnndorff and Leiner. "These varieties (speaking of the above named skin lesions) are not infrequently associated with endocarditis and pericarditis in the most serious cases."

Poynton and Paine⁴ in their "Researches on Rheumatism" (1914), in discussing the cutaneous manifestations of rheumatic fever, note that "In the generalized cases the eruption is often multiform, and in some areas it may be by no means unlike a tinea circinata or erythema iris." They make no further note as to its association with endocarditis or the specificity of the lesion.

William Osler,⁵ notes that in the erythema group of skin diseases cardiac symptoms rarely occurred and that acute endocarditis was a rare complication. Only 3 cases in Osler's series had heart murmurs, and he states that in none of his patients was it likely that endocarditis existed.

If we examine the more recent literature we note that Leichtentritt,⁶ in 1930, recognizes the specific skin lesion, erythema annulare

rheumaticum, and substantiates the findings of Lehndorff and Leiner that it occurs in association with endocarditis. He points out that the occurrence of this lesion is an unfavorable prognostic sign. He feels that even though there be no apparent signs or symptoms, the occurrence of this lesion indicates the persistence of rheumatic infection.

Hans Rietschel,⁷ includes a brief statement concerning erythema annulare rheumaticum and notes that the exanthem has been

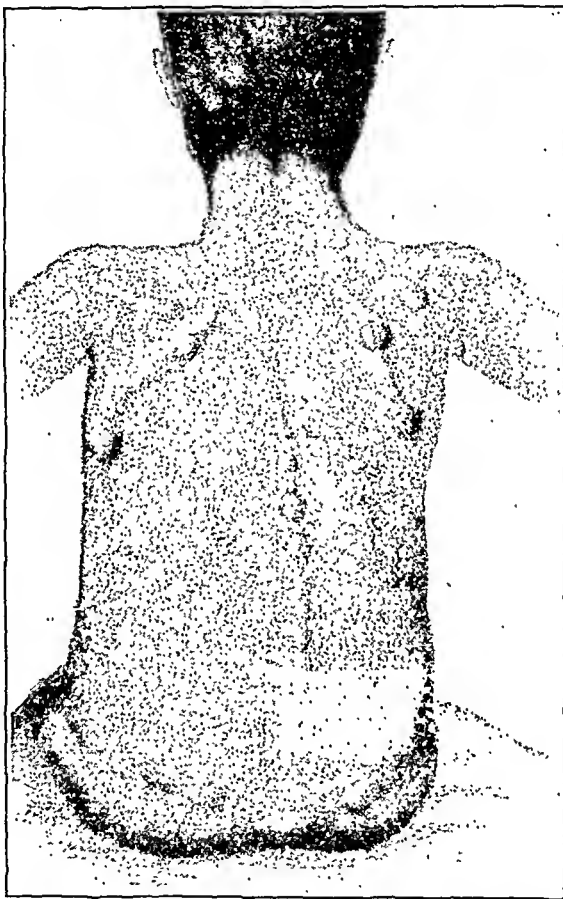


FIG. 2.—Reproduction of frontispiece from Cheadle's "The Various Manifestations of the Rheumatic State" 1889, showing annular rash associated with rheumatic endocarditis, which is termed "Erythema Marginatum."

observed only in endocarditis rheumatica and not in ulcerative endocarditis or subacute bacterial endocarditis.

Poynton and Schlesinger⁸ (1931), devote very little space in their monograph to the subject of the skin manifestations in rheumatism. They make no mention of erythema annulare rheumaticum.

Wilfred Sheldon⁹ notes the following: "*Erythema Marginatum*. This is a characteristic eruption of rheumatism. It appears as numerous slightly raised red streaks which are generally circular,

covering an area about as large as a shilling, or they may coalesce, and then have an irregular wavy outline. The rash occurs principally on the trunk, both back and front, and may also appear on the limbs. It does not itch. It comes out quickly within a few hours, and may be evanescent, or may persist for several days with constantly changing shape. It is likely to recur, and in the author's experience it has always been associated with evidence of cardiac rheumatism."

H. F. Swift¹⁰ states: "The cutaneous manifestations of rheumatic fever consist of various exudative dermatoses, but none is absolutely typical of the disease, as similar rashes are seen in other infections and apparently as independent conditions. Various types of erythema multiforme are the most common; often the rash starts as flat papules, rapidly increasing in size, and clearing in the centers; finally the migratory borders of several lesions fuse into an extensive marginate erythema. Frequently the evolution and resolution occur within a few hours. Often such rashes recur for weeks or months. They commonly do not itch, hence may be easily overlooked. Occasionally purpura is seen."

Griffith and Mitchell¹¹ (1933) write: "Erythema of various sorts is prone to occur, and sometimes purpura, often associated with the arthritis. Purpura rheumatica, so-called, probably has no direct connection with rheumatism."

P. Bertoge¹² (1934) makes but a brief mention of erythema annulare rheumaticum, as described by Lehndorff and Leiner.

Ingerman and Wilson,¹³ in 1924, reported that in 8% of their cases they observed erythema, urticaria and herpes zoster. "To what extent these were actually rheumatic manifestations or only associated conditions in rheumatic subjects, is difficult to determine."

In a recent article on the cutaneous lesions in rheumatic fever Chester and Schwartz¹⁴ (1934) describe lesions mainly on the lateral surface of the legs and on the extensor surface of the forearms. They were rarely seen on the trunk. The lesion was described as consisting of maculopapular purpuric spots, which persisted from 1 to 6 months. The authors further state that the appearance of cutaneous lesions in children who have already had rheumatic fever should be regarded as a manifestation of reactivity. They report 9 cases in which these lesions were observed. In all their patients it is noted that a rheumatic endocarditis existed. Strangely enough, in their review of the cutaneous manifestations of rheumatic fever, they make no mention of the erythema annulare rheumaticum described by Lehndorff and Leiner. In a search through the various treatises on diseases of the skin in skin atlases, no reference can be found to this erythema.

Ormsby¹⁵ states: "The term erythema annulare or circinatum is used to designate the lesions having a depressed center and an erythematous margin forming a ring. Occasionally these rings are arranged concentrically.

"When several rings coalesce by peripheral extension gyrate figures are formed and this is termed erythema figuratum. Erythema marginatum indicates a form in which a distinctly elevated and well defined marginal band is left as the sequel of the erythematous patch. Erythema papulatum or papulosum and erythema tuberculatum or tuberculosum refer to that type of the disorder in which the lesions are papular or nodular."

The various plates in Jacobi's¹⁶ "Atlas of Dermochromes" under the heading of erythemas, have not the slightest similarity to erythema annulare rheumaticum.

Lehndorff¹⁷ has included erythema annulare rheumaticum as a sub-head under "Die Erythemkrankheiten des Kindesalters."

Summary. Erythema annulare rheumaticum (Lehndorff-Leiner) is a specific exanthem associated only with rheumatic endocarditis. The lesions are pale red or bluish-red, semicircles or rings which on first appearance may be from 2 to 4 mm. in diameter and which may develop into rings of 1 to 3 cm. in diameter. The lesions are found on the chest, over the abdomen, on the sides of the thorax, and on the back. They are rarely seen on the extremities and never on the face or mucous membranes. The lesions are never papular but always macular. There is no itching, edema or hemorrhage associated with them. They disappear without scaling or pigmentation.

Lehndorff estimates that erythema annulare rheumaticum occurs in about two-thirds of all cases of rheumatic endocarditis in children. Because of its transitory nature it is often overlooked. The rash is not associated with septic or ulcerative endocarditis or endocarditis lenta, and does not occur in other types of arthritis. It never occurs at the onset of an attack of acute rheumatic fever and only appears following the endocardial involvement. In fact, it so constantly indicates the persistence of a rheumatic infection in association with a cardiac involvement that it has been said rheumatic endocarditis may be diagnosed by merely seeing this rash on the skin. Its prognostic value, in my experience, is varied. In the 1 fatal case here reported it was an ominous sign. In the other 5 children the rash has been noted after illnesses varying from slight colds without febrile reaction, to recurrent attacks of rheumatism with fever.

In the group of children under my observation at the Spaulding School, I have noted this rash more frequently than I have been able to demonstrate subcutaneous nodules. The exact nature of the rash is as yet unknown. No one has as yet established a relationship between this rash and the tuberculin reaction, or the demonstration of tubercle bacilli by gastric lavage, as has been done in erythema nodosum.

Löwenstein and Reitter¹⁸ have demonstrated a tuberculous bacillemia in cases of rheumatic endocarditis with erythema annulare

rheumaticum in Professor Knöpfelmacher's Clinic in Vienna. To date, this finding has not been definitely accepted as evidence of the tuberculous nature of rheumatic fever, and therefore, its significance with regard to rheumatism and the rash must be held in abeyance.

The only reported histologic examination of the skin in a case of erythema annulare rheumaticum, is the one of Carol and Van Krieken.¹⁹ They excised a small area of skin from the abdomen of a 7-year-old girl who was sick with an acute rheumatic fever and an associated rheumatic endocarditis. The child showed the typical erythema annulare rheumaticum described by Lehdorff and Leiner, the rash being most marked upon the abdomen. The exanthem was present at intervals for 12 weeks. The sections of the skin from this case showed on histologic examination, an acute inflammatory process of the outer and intermediate portions of the cutis, consisting nearly entirely of an infiltration of neutrophils. The authors state that this finding differs histologically from the sections of skin examined in cases of urticaria, annulare and erythema exudativum multiforme Hebræ.

Finally it may be concluded that erythema annulare rheumaticum is exclusively associated with rheumatic endocarditis and its appearance has been noted only in association with such cases. The occurrence of this rash in children suffering with rheumatic endocarditis, as is the case with other cutaneous lesions found in this disease, may be considered as evidence of either the persistence of an active rheumatic endocarditis or as a sign of reactivation of the disease.

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SUBCUTANEOUS FATTY NODES IN THE SACROILIAC AREA.

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OF a group of 170 unselected hospital patients, suffering from various complaints, subcutaneous nodes were palpated in the sacroiliac regions in 94 cases. In 45 of them the nodes were present unilaterally; in 49 others they were present bilaterally. The patients varied in age from 2 to 60 years. While the nodules were noted in thin persons, the incidence in stout women past middle age was generally highest. The nodes could be palpated over the sites of the sacroiliac joints; less often they were also present over or near the tips of the lumbar spinous processes (Fig. 1). The nature and character of these nodes were considered worthy of investigation. Since 33 of these patients had low back pains (muscular-skeletal in origin) a correlation was sought between the presence of the nodules and these pains. This was deemed especially appropriate since Stockman contends that inflammatory changes in the subcutaneous fat may be the cause of some of the symptoms referred to muscles or joints.¹ Of the 33 cases with low back pain, 16 had tender subcutaneous nodules in the sacroiliac area, while in 7 others the nodules were not tender.

In 4 cases the nodules were removed in order to ascertain their more intimate nature by gross and microscopic examination.

Case Reports. CASE 1 (Admission No. D1038).—The patient was a woman, aged 50, who complained of severe pains in both lower loins of several months' duration. Occasionally the pains radiated down the posterior aspect of the right leg. Apart from the pain described, the history presented nothing remarkable. Clinical examination revealed tenderness over the right posterior inferior spine of the ilium (an anatomic landmark

for the location of the right sacroiliac joint). Forward bending of the trunk was slightly limited. No hamstring spasm was present in either lower extremity; neurologic examination was negative. Palpation of the sacroiliac regions revealed bilateral groups of subcutaneous nodules. Each side presented clumps of 6 to 8 nodes. They were freely movable under the skin and varied in size from a pea to an almond. The nodes were of the consistency of soft rubber. Those on the right side were very much more tender than those on the left. Roentgenogram of the pelvic bones showed arthritic changes in the sacroiliac joints. Over a period of 4 months the patient received diathermy, baking and local massage; improvement was negligible.

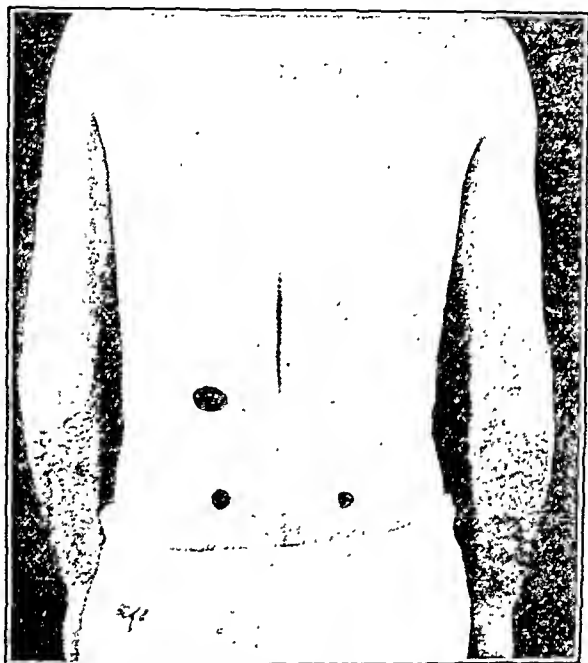


FIG. 1.—Note the location of the subcutaneous nodes.

Clinically the diagnoses considered were lipomas, neurolipomas, peculiarly located rheumatoid nodules, and the so-called myogeloses. The latter are indurations of voluntary muscles. Lange believes them to be the result of local chemical disturbances.² At operation the nodules were found situated (on the right side) on the lower portion of the sacrum near the ilium. A group of 6 nodes was removed from this area. They were composed of lobules of fat, each covered with a thin capsule. Both on gross and microscopic examination, their appearance was that of normal adipose tissue. No indications of inflammatory changes were present. Appropriate stains for nerve tissue showed nothing additional.

Soon after the operation the patient stated her complete relief from all previous symptoms. She was last seen 3 months after the operation, but did not return for additional treatment. No adequate reason for the disappearance of her complaint can be deduced on the basis of the tissue examination. It is hard to conceive what relationship these nodes could have borne to the low back pains.

In an effort to elucidate the concept proposed by Stockman that inflammatory changes in the subcutaneous fat could be a cause of

low back pain, it was decided to remove nodes from patients with obvious foci of infection.

CASE 2 (Admission No. 44950).—The patient, a male, aged 26, has had tuberculosis of the left astragalus for 3 years. In addition to this, clinical examination revealed the presence, bilaterally, of firm, pea-sized subcutaneous nodules over the sacroiliac areas. Low back pain was not present, nor was there any previous history of this complaint; the nodules were tender on palpation.

A subastragaloid arthrodesis was performed. At the same time, a cluster of small nodules was removed from over the left sacroiliac joint. They were composed of adipose tissue, enclosed in delicate capsules. Microscopic examination merely confirmed the gross findings; no evidence of either recent or previous inflammation was disclosed; the thin capsules showed the presence of small arterioles.



FIG. 2.—Photograph of the subcutaneous nodules removed from the sacroiliac area. They consist of lobules of adipose tissue.

CASE 3 (Admission No. 49221).—The patient, male, aged 42, complained of low back pain of 8 years' duration. Various therapeutic measures gave no relief. Clinical examination revealed limitation of forward and lateral movement of the trunk. Neurologic examination was negative. Stumps of tonsillar tissue were infected, and advanced pyorrhea alveolaris was present. Several small subcutaneous nodes could be palpated about 3 inches to the left of the third lumbar spinous process. Although freely movable under the skin, they appeared to be attached to the lumbar fascia. The tenderness in the lumbar and sacroiliac regions was concentrated over the nodes. Roentgenograms of the bones showed arthritic changes in the sacroiliac and lumbar joints.

With a view toward correlating the subcutaneous nodes and the infected tonsils, the nodes were removed. They, too, were found composed of lobules of fat enclosed in thin capsules. The histologic examination showed normal adult fat and a complete absence of any inflammatory changes. The tonsillar stumps were removed one week later. The low back pain still persisted, however, but the area previously tender on palpation was so no longer.

It was further decided to remove nodes from a case which had received no previous local physiotherapy.

CASE 4 (Admission No. D9753).—The patient, a colored woman, aged 29, complained of pain, recent in origin, in the sacroiliac regions, especially

the left. Except for a history of repeated sore throat, her anamnesis presents nothing remarkable. Clinical examination revealed slight limitation of the mobility of the trunk; there was no hamstring spasm; neurologic examination was negative. Tenderness was elicited on palpation of the left sacroiliac region. On less vigorous palpatory examination, groups of subcutaneous nodes could be distinguished bilaterally. Those in the region of the left sacroiliac joint were markedly tender. Radiographic examination of the pelvis disclosed arthritic changes in the joints. The patient had had no physiotherapy.



FIG. 3.—Photomicrograph shows the subcutaneous nodes to be normal adipose tissue covered by vascular capsules ($\times 100$).

The nodes on the left side were removed under local anesthesia. On exposure they were found lying over the distal third of the sacrum close to the posterior inferior spine of the ilium. They were composed of fat and were encapsulated by connective tissue (Fig. 2). The microscopic examination confirmed the gross findings, the fat being normal adult fatty tissue and presented no inflammatory changes (Fig. 3). The clinical complaint did not subside after the operation.

Discussion. As is evident from the pathologic examination of the subcutaneous nodules removed from the sacroiliac regions of several patients, such nodules are composed of lobules of adult fat. The fatty tissue evidences no abnormality, nor is there any indication of inflammation or other evidence that could relate their origin to metabolic or toxic disturbance.³ It would seem that the aforementioned subcutaneous nodules are probably protective or buffer pads over some of the poorly muscle-covered areas of the sacrum and ilium. Their occurrence is not associated with any recognized disease process, and they may be found in apparently normal persons.

Tenderness, often of exquisite degree, over the sacroiliac joints

may be attributed to the mere presence of these subcutaneous fat nodules and not to intrinsic disease in the joints. Of course, in Dercum's disease, lipomas may exist in the sacroiliac regions and cause intense pains of a neurogenic basis. The presence of additional large symmetrical fatty tumors in other parts of the body (in Dercum's disease) helps in differential diagnosis. The subcutaneous nodes discussed in this communication are wholly different from those of rheumatic fever, rheumatoid arthritis, syphilis, and so forth.⁴

The author is indebted to Dr. H. L. Jaffe for many helpful suggestions and to Doctors Finkelstein and Frauenthal for permission to operate on these 4 patients.

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BOOK REVIEWS AND NOTICES

GYNECOLOGICAL AND OBSTETRICAL TUBERCULOSIS. By EDWIN M. JAMESON, B.S., M.D., Fellow of Trudeau Foundation; Attending Surgeon, Saranac Lake General and Reception Hospitals. Pp. 256; 31 illustrations. Philadelphia: Lea & Febiger, 1935. Price, \$3.50.

DR. JAMESON has divided his presentation of this somewhat neglected subject into three main parts, namely: the influence of pulmonary tuberculosis upon the genital physiology, the infections of the genital organs and peritoneum, and the problem of pregnancy in a tuberculous woman. The personal experiences of the Saranac group are incorporated in the study, together with a review and comparison of the ideas and results of other authors. The bibliography is unusually comprehensive. A series of experiments dealing with the routes of infection of the genitalia in animals is described. The author believes the possibility of an ascending type of infection must be taken into serious consideration. The need for premenstrual diagnostic curettage is emphasized. The use of Roentgen ray and radium treatment of pelvic tuberculosis is discussed. The section on pregnancy and tuberculosis reflects a conservative attitude toward the routine interruption of pregnancy, discusses the effects of collapse therapy, and other measures, and furnishes in the conclusions regarding treatment a set of excellent working rules for the physician who meets but an occasional instance of pregnancy and tuberculosis. The scope of the book, the well reasoned deductions, and the clarity of expression will serve to make this book widely read. P. W.

FREE MEDICAL CARE (SOCIALIZED MEDICINE). Compiled and Edited by E. C. BUEHLER, Director of Forensics, University of Kansas. Pp. 360. New York: Noble and Noble, Publishers, Inc., 1935. Price, \$2.00.

THE most important non-professional question for medical men of our time is unquestionably that of socialized medicine and its associated problems. Willy-nilly each physician must take his stand on the subject; but unfortunately many do so under a maximum influence of emotion and a minimum of knowledge of the available facts. This book makes a worthwhile effort to supply this want in an impartial way. It should be valuable not only for the student debaters for whom it was primarily prepared, but also for the chronic debaters in organized medical societies and even for practitioners and medical students seeking unbiased information and arguments on both sides of this complex question. E. K.

MODERN HOME MEDICAL ADVISER. Your Health and How to Preserve It. Edited by MORRIS FISHBEIN, M.D., Editor, Journal American Medical Association, with 23 Collaborators. Pp. 905; 140 illustrations, 4 in color. Garden City N. Y.: Doubleday, Doran & Co., Inc., 1935. Price, \$9.50 (bound in fabrikoid).

HERE is the old "medical book," well known in most homes of a few decades ago, brought thoroughly up to date. Not like its forerunners, given to suggest self-diagnosis and self-treatment to the layman, it is "planned to answer questions concerning all the common, and even some of the extraordinary, illnesses that may develop in any family . . . planned

also as an adequate guide to hygiene and first aid." The 33 chapters also cover such topics as Choice of a Physician, Sex Hygiene, Care of Mother Before and After Childbirth, The Hazards of Industry, Advice on the Diet, Nervous and Mental Disorders, Old Age. In addition to Dr. Fishbein there are 23 contributors, eminently qualified to handle their particular subjects, and including such well-known authorities as Elliott P. Joslin, Russell M. Wilder and Francis Carter Wood. Physicians will welcome this book, written in language that anyone can understand, as one they can heartily recommend to all laymen. Minor query: why not state the degree of magnification used in the picture of the Black Widow Spider (*Latrodectus* misspelled in text)?

R. K.

THE PROBLEM OF MENTAL DISORDER. A Study Undertaken by the Committee on Psychiatric Investigations, National Research Council. Members of the Committee: MADISON BENTLEY, Chairman, Sage Professor of Psychology, Cornell University, and E. V. COWDRY, Professor of Cytology, Washington University. Pp. 388. New York: McGraw-Hill Book Company, Inc., 1934. Price, \$4.00.

THIS volume was made possible through a grant of the Carnegie Foundation and through the excellent editorship of Professors Bentley and Cowdry—neither a psychiatrist, but both pure scientists, first-rank psychologist and cytologist respectively, and both well able to speak of psychiatry and its supportive sciences. It is these latter for which the bulk of this book is reserved. The first section, "The Character of the Problem," is a well written statement of the status of present-day psychiatry in all its manifold aspects, and of the suggested outlines of methods for solving its problems. Section Two, "Current Points of View," is an exposition of contemporary viewpoints of psychiatric thought, each propounded by an eminent representative; namely, C. MacFie Campbell ("Clinical"), A. Meyerson ("Medical"), I. S. Wechsler ("Neurological"), A. Meyer ("Psychobiological"), and L. S. Kubie ("Psychoanalytical"). Within Section Three, "Supporting Sciences: Present-day Contributions and Future Research," are compressed 20 short contributions by investigators in the sciences, including anatomy, physiology, chemistry, genetics, education, sociology and anthropology, etc. With the ambits of psychiatric theory and research continuously expanding, and with the anatomizing of related knowledge into even more complex secondary problems, such a critique does great service in bringing together the accumulated, unwieldy mass of uncorrelated data into the semblance of an intelligible whole, and in providing some measure of comforting orientation in the midst of confusion. This book deserves a wide distribution.

P. R.

AN OUTLINE OF IMMUNITY. By W. W. C. TOPLEY, M.A., M.D., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology in the University of London. Pp. 415; 37 illustrations and 63 tables. Baltimore: William Wood & Co., 1933. Price, \$6.00.

THE author intended this book for the medical student, believing that "ignorance of the present working hypotheses of immunity means inability to form a sound judgment on many severely practical problems." The subject matter reveals incisive and comprehensive thinking. So careful is the presentation and criticism of data that it will be of service to the life-long student of medicine who also practises it. The Reviewer wishes particularly to commend the method of presentation. The first subject to be considered, and one too often neglected, is the nature and significance of the evidence obtainable in this difficult field, and the necessity in many

cases for the application of simple statistical methods in the criticism of results and the planning of experiments. Neglect of this has vitiated many a series of experiments. Without such a criterion it may be impossible to evaluate the therapeutic usefulness of a serum where the effect is not dramatic. The history of the use of antipneumococcal serum is a case in point (pp. 366-369). About a hundred pages are devoted to a useful summary of methods of standardizing immunologic reagents and their use in the diagnosis, treatment and prevention of disease. The practitioner should note that the book appeared in 1933, and therefore, is not always up to date. Suggestive work on the streptococci in puerperal fever, for instance, has since been done (p. 111).
D. S.

A SYNOPSIS OF REGIONAL ANATOMY. By T. B. JOHNSTON, M.B., CH.B., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 460; 11 illustrations. Third edition. Philadelphia: Lea & Febiger, 1935. Price, \$4.50.

THIS third edition represents little change from previous editions. The glossary of the B.N.A. has been revised and is probably one of the most useful sections of the book. The anatomy is discussed by regions with no illustrations, except 11 line drawings of the anatomy of the central nervous system. The book should be useful as a quick reference for students and practitioners.
L. F.

NEW BOOKS.

Clinical Parasitology and Tropical Medicine. By DÁMASO DERIVAS, B.Sc. BIOL., M.S., M.D., PH.D., Professor of Parasitology in the Graduate School of Medicine and Assistant Professor in the Department of Pathology, University of Pennsylvania; Pathologist to the Pennsylvania Department of Health, The Friends' Hospital, and the Skin and Cancer Hospital, Philadelphia, etc. In Collaboration with CARLOS T. DERIVAS, B.A., M.D., Pathologist to the Santo Tomas Hospital, Panama, etc. Pp. 367; 144 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1935. Price, \$5.00.

Body Water. The Exchange of Fluids in Man. By JOHN P. PETERS, M.D., Professor of Internal Medicine, Yale University School of Medicine. Pp. 405; 5 illustrations and 15 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, \$4.00.

Modern Home Medical Adviser. Your Health and How to Preserve It. Edited by MORRIS FISHBEIN, M.D., with 23 Collaborators. Pp. 905; 140 illustrations, 4 in colors. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1935. Price, \$9.50 (bound in fabrikoid). (Review, p. 838.)

Beitrag zur Kenntnis des Ileum Terminale Fixatum und Ileus Ilei Terminalis Fixati. Eine anatomische, klinische und klinischstatistische Studie. (Vol. 75, Supp. 32 of Acta chirurgica Scandinavica.) By LENNART PETERSON. Pp. 113; illustrated. Helsingfors: Mercators Tryckeri Aktiebolag, 1934. (No price given.)

Free Medical Care (Socialized Medicine). Compiled and Edited by E. C. BUEHLER, Director of Forensics, University of Kansas. Pp. 360. New York: Noble and Noble, Publishers, Inc., 1935. Price, \$2.00. (Review, p. 838.)

Grundzüge der praktischen Seelenheilkunde. By DR. MED. FRITZ KÜNKEL, Berlin. Pp. 168. Stuttgart: Hippokrates Verlag G.M.B.H., 1935. Price, Rm. 6.75, paper binding; Rm. 8, linen binding.

International Clinics. Vol. III, Forty-fifth Series, 1935. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 337; illustrated. Philadelphia: J. B. Lippincott Company, 1935.

One medical and three surgical papers, together with progress articles on ophthalmology and otolaryngology comprise this number. The international element is maintained by Parkes Weber's "Carcinoma Telangiectaticum" and Loeser's (of Freiburg) paper on the pituitary and thyroid.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University School of Medicine. Pp. 551; 121 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, \$5.00.

Individual Exercises. Selected Exercises for Individual Conditions. By GEORGE T. STAFFORD, M.S., Director, Corrective Physical Education, University of Illinois, HARRY B. DECOOK, M.A., Director, Corrective Physical Education, Northwestern University, and JOSEPH L. PICARD, M.S., Director, Corrective Physical Education, University of Arizona. Pp. 111; 100 illustrations. New York: A. S. Barnes & Co., Inc., 1935. Price, \$1.00.

"In recent years the question of exercise has become of vital interest. It is not unusual for a physician to prescribe 'exercise' as well as medicine. Individuals of their own accord are seeking health through exercise. School boards consider physical education as an integral part of education—rather than a frill or a fad. The difficulty comes in determining what kind, type or amount of exercise one should take. . . . Hence, this book is written, avoiding technical language as far as possible, with the idea of giving the reader basic information regarding exercise for individual needs. . . . The doctor, the physiotherapist, the physical educator and the teacher will find this book helpful in selecting exercises for the large number of individuals who, because of physical defects, deformities, etc., should not be permitted (or are not able) to take the regular physical education work." (From Authors' Preface.)

Mechanics of Normal and Pathological Locomotion in Man. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City. Pp. 424; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, \$8.00.

The Stomach and Duodenum. By GEORGE B. EUSTERMANN, M.D., F.A.C.P., Head of Section in Division of Medicine, The Mayo Clinic; Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, and DONALD C. BALFOUR, M.B., M.D. (Tor.), LL.D., F.A.C.S., F.R.A.C.S., Head of Section in Division of Surgery, The Mayo Clinic; Professor of Surgery, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, and Member of the Staff, The Mayo Clinic and The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 958; 436 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, \$10.00.

A Marriage Manual. A Practical Guide-Book to Sex and Marriage. By HANNAH M. STONE, M.D., Medical Director of the Birth Control Clinical Research Bureau and of the Marriage Consultation Centers at the Community Church and Labor Temple, New York, and ABRAHAM STONE, M.D., Adjunct Urologist at the Sydenham Hospital, Co-Director of the Marriage Consultation Centers at the Community Church and Labor Temple, New York. Pp. 334; 8 illustrations. New York: Simon and Schuster, 1935. Price, \$2.50.

Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes and Tonsils. By FRANCIS H. WILLIAMS, M.D. (Harv.), S. B. Massachusetts Institute of Technology; Senior Physician, Boston City Hospital; Fellow of American Academy of Arts and Sciences, etc. Pp. 118; 12 illustrations. Boston: The Stratford Company, 1935. Price, \$2.00.

Diabetes, The Malady of Our Time. A Manual. Etiology, Course and Treatment of "Diabetes Mellitus." By DR. LEVY-LENZ and DR. HEINZ SCHMEIDLER. Pp. 64; illustrated. Berlin: A. K. Verlag (Arthur Kirchner), 1935. Price, \$1.15.

Genetics. By H. S. JENNINGS, Henry Walters Professor of Zoölogy and Director of the Zoölogical Laboratory in the Johns Hopkins University. Pp. 373; 70 illustrations. New York: W. W. Norton & Co., Inc., 1935. Price, \$4.00.

Diseases of the Nose and Throat. For Practitioners and Students. By CHARLES J. IMPERATORI, M.D., F.A.C.S., Professor of Clinical Oto-laryngology, New York Post-Graduate Medical School, Columbia University, and HERMAN J. BURMAN, M.D., Instructor of Clinical Oto-laryngology, New York Post-Graduate Medical School, Columbia University. Pp. 723; 480 illustrations, some in colors. Philadelphia: J. B. Lippincott Company, 1935. Price, \$7.00.

NEW EDITIONS.

The Pathology of Internal Diseases. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CAN.), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 904; 335 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1935. Price, \$10.00.

Laboratory Methods of the United States Army. Edited by JAMES STEVENS SIMMONS, B.S., M.D., PH.D., Major, Medical Corps, U. S. Army; Director of Laboratories, Army Medical Center; Director of the Department of Preventive Medicine, Army Medical School. Associate Editor, CLEON J. GENTZKOW, M.D., PH.D., Major, Medical Corps, U. S. Army; Chief of the Division of Chemistry, Army Medical School. Approved by the Surgeon-General of the U. S. Army. Pp. 1089; 70 illustrations and 133 tables. Fourth Edition. Philadelphia: Lea & Febiger, 1935. Price, \$6.50.

"Although the title of this work is 'Laboratory Methods,' its scope has been enlarged to include material other than strictly technical procedures. For example, in the section on Bacteriology, tables of classification and brief summaries of the more important characteristics of certain bacteria have been added; and the sections dealing with Protozoölogy, Helminthology and Entomology have been expanded and include illustrations of certain organisms. New sections, one dealing with Rickettsia and Filterable Viruses and another with Statistical Methods, have been added." (From Author's Preface.)

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, M.D. (HARV.), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the coöperation of HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., and ALEXANDER MARBLE, M.D. Pp. 620; 7 illustrations and 144 tables. Fifth Edition, revised and rewritten. Philadelphia: Lea & Febiger, 1935. Price, \$6.00.

Personal and Community Health. By CLAIR ELSMERE TURNER, M.A., DR. P.H., Professor of Biology and Public Health in the Massachusetts Institute of Technology, etc. Pp. 680; 130 illustrations, 4 colored plates and 13 tables. Fourth Edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$3.00.

Diseases of the Skin. By FRANK CROZER KNOWLES, M.D., Professor of Dermatology, Jefferson Medical College; Dermatologist to the Jefferson, the Pennsylvania, the Presbyterian and the Babies' Hospitals, etc. Pp. 640; 240 illustrations and 11 plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, \$6.50.

PROGRESS OF MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
FRANKLIN G. EBAUGH, M.D.,
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
GEORGE JOHNSON, M.D.,
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FUNCTIONAL LOCALIZATION IN THE CEREBRAL CORTEX.

THE study of functional localization in the brain may properly be said to begin, along with most other beginnings in medicine, with Hippocrates. In his treatise on "Wounds of the Head" he described various kinds of fractures and warned against incisions into the brain so as not to produce convulsion on the opposite side of the body. Galen taught that the cerebrum is the organ of intelligence and conscious sensations and apparently did ablation experiments on the cortex to study its function. At this time, however, and for many centuries after Galen, the ventricles were considered to be the principal centers for localized function; thus the anterior contained imagination, the middle reason and the posterior memory. In the 17th century Willis made some significant observations on the concept of cerebral localization and during the same century Wepfer¹ first accurately described cerebral apoplexy and hemiplegia. It was not until the latter part of the 19th century however that real progress in the study of cerebral function was made. The work of Hitzig and Fritsch,² and of Ferrier³ on the electrical stimulation of the exposed cerebrum of the living animal marks the beginning of our modern views. The first effect of the work of these investigators led to extreme views of localization of function in which different motor and sensory areas were thought to be definitely circumscribed. Cortical diagrams were numerous with different centers plotted for various functions, each center specific in purpose and sharply separated from every other in a mosaic pattern.

The development from this concept of localization of function to sharply limited areas to the present-day concept is well expressed by de Barenne⁴ in his criticism of the use of the term localization of function. He writes, "An enormous number of nervous activities involve not only the cortex but also other levels of the nervous systems. This is true of the human being, so far as is known, for all perceptual and

voluntary activity. This means, irrespective of one's point of view in regard to the problem of functional localization within the cortex, that it is incorrect to state that vision, hearing or motility is 'localized' in the cerebral cortex. If this term is used, the only appropriate statement would be that the nervous function under consideration is 'localized' in all those nervous structures which are thrown into activity in the performance of the function." The central nervous system has come to be looked on as a highly integrated mechanism each cell of which has a demonstrable function to perform not as an independent entity but as a unit essential for the successful operation of the mechanism as a whole.

Although this point of view has gradually developed during the past 60 years, notably through the contributions of Sherrington,^{5,6} Beevor and Horsley,⁷ Brodmann,⁸ the Vogts,⁹ significant contributions have been made during the past year especially in the studies of Fulton and his group on the frontal lobe.

The Frontal Lobe. From the standpoint of functional activity the frontal lobe may be divided into four well-defined areas. As defined by Fulton¹⁰ these areas are:

1. The motor area beginning in the depths of the central sulcus and extending rostrally on the lateral surface. The limits of the motor area are determined by its cellular structure, being the region of the cortex containing in its fifth layer the large cells of Betz which give rise to the pyramidal pathways.¹¹
2. The premotor area comprises the region of the cortex anterior to the motor area. It is histologically identical with the motor area apart from the absence of the large motor cells in the fifth layer. In man the premotor area occupies a much larger part of the exposed surface of the hemisphere than does the motor area.
3. The frontal eye fields. These are a specialized part of the frontal lobes, concerned with coördinated eye movements.
4. The frontal association areas, or the pre-frontal area.

The Motor Area: (Area 4). It is a time honored conception that a destructive lesion of the motor cortex always produces contralateral paralysis accompanied by heightened tendon reflexes, spasticity and finally contractures. Experimental evidence and clinical data cast considerable doubt upon this conception. Studies of the response to electrical stimulation of the motor cortex shows that the resultant movement is of a discrete type, generally one produced by a single muscle. The response is distinctly focal. Only if the stimulus is very strong or if the threshold stimulus is continued over a long period does the movement spread to adjacent muscles, producing the traditional "march" of the Jacksonian focal seizure. Furthermore, stimulation of a point at the anterior margin of the motor area produces movements of the ipsilateral lower extremity. In ablation experiments, a unilateral lesion sharply restricted to the motor area causes immediate and complete paralysis of voluntary movement for a period varying from 2 days to a week. During this period the limbs are flaccid with diminished or absent reflexes, and marked muscular wasting may appear. Voluntary motor power gradually returns, appearing first at the hip and the shoulder and gradually extending to the knee and ankle and finally to the digits. The deep reflexes gradually reappear. The

Babinski and Chaddock reflexes develop when the deep reflexes return. There is no loss of memory or mental confusion even when the pure motor area lesion is bilateral.

Premotor Area: (Area 6). From the point of view of electrical excitability, the premotor area may be divided into anterior and posterior parts (Areas 6a Alpha and 6a Beta). From the posterior part movements of individual muscles may be obtained which are similar but somewhat less discrete than those obtained from the premotor area. These discrete movements cannot be evoked after the motor area has been destroyed or after the cortex has been superficially incised between the motor and the premotor area: the movements are therefore dependent upon the integrity of the pyramidal fibers. From the entire premotor area, complex and seemingly purposeful movements are to be observed which effect not single muscles but an entire extremity or the whole half of the body. These responses involve patterns of movement rather than the reactions of single muscles. They are generally associated with turning the head and eyes to the opposite side and with torsion of the pelvis. All of this reaction persists after incision of the cortex between Areas 4 and 6 and after complete degeneration of the pyramidal tracts. They disappear when Area 6 is undercut. The reactions therefore clearly involve the extrapyramidal motor projection systems arising in the premotor area.^{12,13} Following isolated removal of the premotor area profound motor disability occurs which lasts both in man and in the chimpanzee for 4 or 5 days. Immediately after such a lesion the affected extremity becomes highly spastic; no wasting occurs, electrical excitability is normal and certain characteristic pathologic reflexes such as forced grasping,¹⁴ the fanning sign of Babinski and the sign of Rossolimo, Mendel, Bechterew and Hoffman develop. There is also profound vasomotor disturbance, the affected side losing for a time its power of reflex vasodilation and sweating.¹⁵ Voluntary power begins to return simultaneously in all parts of the extremity generally in 4 or 5 days but skilled movements such as those necessary to play the piano, to finger a violin or to tie a shoe lace become permanently impaired.¹⁶ In trained animals there is considerable intellectual deficit in that they forget problem box manipulations but reeducation is possible (Jacobsen^{17,18}).

Frontal association area or pre-frontal area: No movements of the extremities or of any other of the bodily structures are obtained by stimulation of these areas. Removal of one frontal area causes no recognizable deficit, intellectual or neurologic unless the eye-fields are encroached upon in which case the animal is unable for about 48 hours to carry out conjugate lateral deviation of its eyes to the site of the lesion. Bilateral ablation of the frontal association areas is also without effect upon reflexes, motor power or posture but it has a profound influence upon the behavior and the capacity to learn and remember complex problems. The animal becomes very restless and easily distracted and previously acquired patterns of response in problem situations deteriorate and the animal cannot be retrained. No dominance of lobes is noted in lower animals. In summary, Fulton makes the following conclusions as a result of experiments on the cortex of trained monkeys and chimpanzees.

1. Electrical excitability is present in the motor, premotor and eye

fields but not in the frontal association area. The excitability of the premotor area persists after complete removal of the motor area and degeneration of the pyramidal tracts. Movements of the ipsilateral lower extremities can be obtained from the premotor region.

2. Ablation of the motor area causes flaccid paresis with depression of the reflexes. Voluntary power invariably returns however in all four extremities, after the motor area has been completely removed from both sides.

3. Ablation of the premotor area causes transient spastic paresis with forced grasping and increase in all the deep reflexes. Combined ablation of motor and premotor areas cause permanent spasticity as in capsular hemiplegia but not complete loss of power.

4. Removal of motor and premotor areas from both hemispheres is followed by complete and permanent loss of voluntary power (cortical paralysis) and the postural reflex status of such a preparation is identical to that of a thalamus animal.

5. If a part of one motor or premotor area of one hemisphere remains intact the animal is able to carry out cortically innervated movements in all four extremities. This, together with the observations on stimulation, indicates that ipsilateral representation exists in both the motor and premotor regions.

6. Removal of the premotor area gives rise to vasomotor disturbance on the opposite extremities and to other signs of impairment of the autonomic function.

7. Bilateral removal of the frontal association areas causes no paresis or reflex disturbance but it causes loss of memory for complex skilled acts and an incapacity to profit by recent experience.

In a summary of the clinical interpretations of these phenomena, Fulton and Viets¹⁹ make the following conclusions:

1. Lesions restricted to the pyramidal tracts or to their cells of origin cause flaccid motor paralysis, muscle atrophy, transient depression of all reflexes and the positive signs of Babinski and Chaddock; after complete destruction of the pyramids, the signs of Babinski and Chaddock persist permanently but the paralysis flaccidity and reflex changes tend with time to disappear.

2. Lesions of the premotor projection area of the cortex, which also indicate voluntary movements give rise to spastic paralysis, disturbance of skilled movements, forced grasping, vasomotor disturbance, increased deep reflexes and the signs of Rossolimo, Mendel, Beehterew and Hoffman. Forced grasping and vasomotor disturbance are transient but disturbances of skilled movements and the signs of Rossolimo and Hoffman tend to persist.

3. Hemiplegia in man is generally produced by combined destructions of motor and premotor components of the upper motor neuron and hence such cases generally exhibit combinations of the foregoing symptoms with more severe ultimate motor paralysis than when only the pyramidal tracts are involved. The prognosis can be inferred from the extent to which the two systems are involved.

Aphasia. Another noteworthy contribution to the understanding of functional localization was the publication by Weisenburg²⁰ of the results of his 4-year study of aphasia. From a group of 314 patients 60 were selected for study on the basis of: Clearcut aphasia, age under 60, English as a mother tongue and adequate sight and hear-

ing. A comprehensive group of tests so designed as to cover a wide field of language and mental functioning was given to this group and to an additional control group of 85 normal adults, comparable to the aphasic group in age and in educational, occupational, and social classes. The most satisfactory classification of aphasic disorders according to this study is (a) the expressive, (b) the receptive, (c) the expressive-receptive, and (d) amnesic. Of the four the amnesic represents the only fairly clearcut syndromes. The disorders of the first two groups are only predominantly expressive or predominantly receptive; in the expressive there is always some degree of limitation in receptive functions and in the receptive there are always some defects in speaking and writing.

(A) The predominantly expressive disorders handicap speaking and writing more seriously than the receptive functions. They are characterized most obviously by defects in articulation and word formation but they may involve extensive changes in many language and non-language performances.

(B) The predominantly receptive disorders involve relatively serious defects in the understanding of spoken language or of printed material. Expressive disturbances also appear but are almost always less prominent than the receptive; they consist largely of verbal and grammatical confusions.

(C) The expressive-receptive disorder is a severe limitation in all language processes with or without considerable disturbances of non-language performances.

(D) The amnesic disorder is a fundamental difficulty in evoking words as names for objects, conditions or qualities and is manifested in many language responses. From this classification it is apparent that aphasia is not a unitary disorder but a group of disorders representing different types of disintegration within the language process and sometimes involving changes in mental functioning beyond the language process.

In this study the term apraxia was limited to disturbances in familiar and more or less automatic acts which do not depend on sensorimotor defects. Agnosia was limited to disturbances in the perception of formerly well known objects, forms and sounds when there are so sensory defects to explain the disturbances. There are two types of apraxia, one involving movements of the muscles of speech and the other familiar acts such as manipulating an object. Some of the aphasic patients were unable to take positions of the lips, teeth and tongue at command or by imitation when the production of actual sounds was not in question. The apraxic symptoms of the other type appeared in cases of general deterioration with aphasia or in cases of bilateral lesion.

Agnosic disturbances in the recognition of well known sounds other than speech sounds, of objects, or of forms other than letter symbols were not found in patients of the aphasic group. There is a definite dominance of the hemispheres not shown in lower animals as indicated by the evidence that the dominances indicated by handedness is a criterion of the crucial hemisphere for speech in about 95% of the cases. From the clinical symptomatology and pathologic evidence in the expressive cases, the lesions were predominantly in the anterior portion of the brain and to a less extent in the parietal and temporal zones. In the receptive cases as a group the neurologic symptoms also indicate

a preponderant implication of the anterior part of the brain, but less than in the expressive cases and with a greater involvement of the parietal and temporal zones. In the expressive-receptive cases, the neurologic symptoms point strongly to implication of the anterior part of the brain but because of the patient's great language difficulties little can be determined about the extent to which posterior areas are involved.

It is the opinion of Weisenburg that it is very much a question whether it will ever be possible to localize from the anatomic standpoint the causes which lead to aphasic disturbances. The disorders in aphasia go beyond speech disturbances, and the complex processes affected depend on the function of the whole brain.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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SUPPURATION OF THE PETROUS PYRAMID.

PETROSITIS, petrosal tip suppuration, and suppuration of the petrous pyramid are terms which have been applied to a syndrome occurring during the course of an acute otitis media or mastoiditis. The pathologic basis for the clinical picture is a suppurative process within the pneumatic cells of the petrous portion of the temporal bone, or an osteomyelitis of the pyramid. For years reports of inflammatory lesions located in the petrous pyramid have appeared in the literature. These in the main have been in the nature of unusual findings at autopsy of meningitis deaths of otogenic origin. Macroscopic and microscopic descriptions of various fistulæ leading from the middle ear to the meninges constituted the main body of the reports as a rule. For some reason the clinical symptomatology of such lesions, and what is more important, the clinical sequence of events that led to the terminal meningitis received but scant attention. It is true that the Gradenigo syndrome, consisting of pain in the distribution of the trigeminal nerve associated with external rectus palsy and otorrhea, has had extensive otologic recognition, and the occasional complication of meningitis was also well known. It remained for the classic and monumental work of Kopetsky and Almour¹ definitely to establish petrositis as a clinical entity by minutely describing the anatomic basis for the lesion, its specific pathology, its symptomatology and characteristic course, diagnostic criteria, and last, but not least, an operative technique for dealing effectively with the process in order that a fatal meningitis be prevented. Since that time suppuration of the petrous pyramid has assumed a deservedly prominent place in the otologic literature, as is evidenced by the large number of contributions dealing with the condition that have appeared all over the world in the past few years.

Anatomy. Examination of a well pneumatisized temporal bone discloses the fact that the pneumatic cells are not confined to the mastoid portion but are seen to invade the zygoma, the squama, the floor of the middle ear, the tegmen and also the petrous tip. These cells, occupying portions of the temporal bone other than the mastoid, bear the same developmental relationship to the middle ear as do the mastoid cells themselves, and for that reason can well become involved in a suppurative process originating in the middle ear. Most investiga-

tions have shown that the petrosal pyramid frequently presents a structure similar to that of the mastoid itself. Thus a well pneumasized mastoid process is frequently associated with a well pneumatisized petrosa, while diploic and sclerosed mastoids usually accompany similarly constituted petrous tips. Pneumatization of the petrous apex does not appear as frequently as has been supposed. Myerson² and his co-workers described such a condition in but 11% of 200 temporal bones studied. They also found that the cellular structure of the petrous pyramid and the mastoid were not always alike, as 25% of the mastoids were pneumatisized, as compared with the 11% of the tips. As the cases reported by Kopetsky and Almour occurred in fully pneumatisized mastoids associated with cellular petrous tips, the importance of these findings is obvious; for a non-cellular pyramid cannot undergo coalescence and contain within its anatomic confines a frankly purulent collection. Profant,³ in a study of 50 adults, concluded that as a rule a well developed mastoid had a well developed petrous, and one with a sclerotic mastoid had a sclerotic petrous pyramid. Belinoff and Balan⁴ found pneumatisized tips in 38% of 40 temporal bones studied. Hagens,⁵ in a study of 25 bones in gross section and a similar number microscopically, found that 28% of the gross specimens had a pneumatisized apex. Ramadier⁶ divides the cells into an intrapetrosal group and a supralabyrinthine group, and Lange⁷ describes similar cell tracts.

Pathology. In the original report by Kopetsky and Almour,¹ the petrous lesion was described as a coalescent osteitis of the cells in the petrous tip, which they believed to constitute a distinct pathologic entity. The avenues of infection mentioned by them were: (1) From the antrum or epitympanic space, above or below the superior semicircular canal, following the postero-superior surface of the petrosal into the tip; (2) via the peritubal cells into the tip; (3) via the peritubal cells directly into the carotid canal or through dehiscences in the anterior tympanic wall into the carotid canal.

These avenues can be recognized macroscopically at postmortem or at the operating table. Microscopic examination disclosed the pathway to be along the perilabyrinthine cells originating in the antrum or epitympanum. Friesner and Druss⁸ also mention the peritubal route. The end result of the spread of the infection is the development of an abscess or empyema of the petrous tip if it be cellular in nature. If, on the other hand, the tip is diploic in character an osteomyelitis will result, as has been described by Eagleton.⁹ The extension of the inflammation to the superior surface of the tip involves the Gasserian ganglion with the production of the typical distribution of pain. A subdural abscess may develop, or, as frequently occurs, the lesion may spread to the meninges with the development of a fatal meningitis. The suppurative process appears to spread by way of the perilabyrinthine tracts, as the mastoid and middle ear infection tends to clear up and disappear. At times the petrous suppuration may discharge into the middle ear by rupturing through cells around the Eustachian tube. This fact can account for the characteristic observation in petrositis of the sudden occurrence of profuse discharge after an interval of a dry ear, and also explains some of the cases in which spontaneous cure has been observed.

Probably the most outstanding pathologic manifestation in petrous

suppuration is the fistulization leading from the middle ear or mastoid into the petrosa. It has been the subject of a great deal of interest in most reports that have dealt with the operative or autopsy findings in this condition. Myerson, Rubin and Gilbert³⁶ were able to collect 53 cases from the literature in which such fistulae were observed and recorded. Twenty-nine of these tracts were found in relation to the superior semicircular canal, 18 were found in relation to the Eustachian tube, being located at the tubal orifice or peritubal. Five were found just below the posterior canal, 4 at the arch of the superior canal and 1 behind the posterior canal. We thus have a clue as to the probable location of a fistula and where it must be sought at the time of operation. The varying sites of the fistulae may also explain why no one surgical procedure could be applicable to all cases.

Symptomatology. The characteristic picture of petrous suppuration is exhibited by a patient afflicted with a prior acute suppurative middle ear infection or mastoiditis, who complains of a pronounced and profuse recurrence of the otorrhea and the appearance of pain on the same side at about the same time. The pain, as a rule, is limited to the eye or the orbit and is described by the patient as in or back of the eye, the location and character being almost diagnostic in significance. There is present a low grade sepsis, the temperature ranging from 99 to 102°. The pain, discharge and sepsis, as a rule, appeared after a quiescent interval varying from 5 days to several weeks, during which no pain was present, and in which the ear had become dry or almost so and in which the temperature showed but little rise above normal. The Roentgen ray reveals two important findings, a highly pneumatisized mastoid and petrous tip and a suppurative lesion in the latter. It is to be noted that abducens paralysis is not mentioned and the lesion is therefore not to be confused with Gradenigo's syndrome as has frequently occurred in the reported literature. Perrone,¹¹ reporting 3 cases, states that only infrequently is the Gradenigo syndrome caused by a petrous suppuration. Takaski,¹² Retjo,¹³ Mounier-Kuhn,¹⁴ Ballenger,¹⁵ and Piquet,¹⁶ all report cases with abducens palsy but with no evident petrosal lesions. Yet external rectus paralysis does occur in some cases of petrositis, as evidenced by the reports of Lemaitre and Lemoine,¹⁷ Seydell,¹⁸ Blassingame,¹⁹ Bernstein,²⁰ Galtung,²¹ Rutin,²² and Moulon-guet and Pierre.²³ Undoubtedly the appearance of the rectus lesion was an expression of meningeal involvement from the suppurating petrous pyramid. Apparently petrosal suppuration may occur with or without abducens paralysis. The explanation of the pain in and about the eye was that it was consequent to an irritation of the ophthalmic branch of the fifth nerve. Studies by Vail²⁴ led him to believe that the pain was caused by the great petrosal nerve rather than the ophthalmic branch of the trigeminal. Eagleton,⁹ however, explained the irritation of the ophthalmic branch of the fifth nerve as being due to tension on the dura surrounding the nerve by the edema and swelling consequent to the inflammatory process in the adjacent bone. Myerson and his coworkers¹⁰ believe that the recurrent tentorial branch of the ophthalmic division to be the explanation of the phenomenon. Paralysis of the seventh nerve has been described, Myerson *et al.* having 3 cases and Kopetsky,¹ Profant,³ and Friesner and Druss,⁸ also report such cases. The discharge as a rule is profuse, although it may be

scant or absent. The discharge is large in amount when a fistulous tract from the petrous is emptying the exudate into the middle ear or mastoid. If the fistula is blocked by granulations the otorrhea diminishes and becomes scant or absent. If no fistula is present little, if any, otorrhea may be seen. As the suppuration is contained within the perilabyrinthine cells it is not unusual to find some cases evidencing symptoms of labyrinthine irritation. These are usually vertigo and nystagmus. Functional examination of the labyrinth is negative, showing the lesion to be a perilabyrinthitis. The laboratory findings are those of a mild infection. A leukocytosis of 9000 to 14,000 may be present. The organisms responsible for the infection are similar to those found in any mastoid infection. Rollin²⁵ and Fowler²⁶ report petrous infections due to the well known virulent pneumococcus Type III.

The Roentgen ray is of great importance and must be considered one of the guiding signs in the management of the disease. Caution must be exercised in the interpretation of the Roentgen ray films. Sussman²⁷ believed that the picture taken in the Stenver position was most useful. Epstein²⁸ preferred 3 exposures by the methods of Schuller, Mayer, and Stenver. Probably the method of Taylor²⁹ is the safest to follow. He takes a base plate showing both petrous tips early in the course of the otitis and files this for future reference. If later in the course significant clinical phenomena appear, another base plate and a Stenver plate are taken. By comparison with the early base plate, significant changes in the petrosa may be established.

Treatment. The therapy of petrous suppuration is surgical. The manner of approach and the type of surgery to employ must vary somewhat with the nature of the lesion. Whatever method is undertaken, it is assumed that it must be adequate in eradicating the suppurating focus and preventing extension of the disease to the meninges with a possibly fatal outcome. Various techniques have been advocated. Voss³⁰ believed that, in addition to the performance of the mastoid exenteration, a wide exposure of the epitympanum would be sufficient to drain the petrosa. Undoubtedly the exposure of a fistula without enlarging its opening will but rarely cause it to drain satisfactorily. Many cases in which no apparent fistula can be observed have been described and such cases of course require further surgery. This type of surgery is certainly far from convincing as to its adequacy in the various types of purulent retention in the petrous pyramid. Frenckner³¹ enters the petrous tip through the arch of the superior semicircular canal, removing the cancellous tissue between the horizontal and superior canals with a specially constructed curette, outlining the arch and following the cells beneath the arch, forward and inward until the tip is entered. If a fistula is present at the time of operation, it would seem wiser to utilize this tract established by Nature to drain the tip by widening and enlarging it. Even when confronted by a closed empyema of the tip, this procedure may be found wanting as the presence of a tract of cells beneath the arch is not constant and one may have extreme difficulty in producing a tract through the dense bone. Ramadier, Guillon and Becker³² describe a rather formidable procedure which they developed on the cadaver. The technique entails an extensive wide radical mastoid operation, removing the anterior bony

canal wall as well as the floor, exposing the glenoid fossa and the anterior wall of the middle ear which is removed below the opening of the Eustachian tube, thus exposing the carotid artery which is pulled out of its canal by means of a ligature, enabling the operator to enter the petrous tip through the inner wall of the carotid canal. Such a radical procedure is open to a serious question. The mandibular joint may have interference with its function as a result of the operation. Post-operative drainage from the tip may be impeded by the carotid artery falling back into place at the termination of the procedure, and the technique may also open other pathways of septic soilage of the meninges by way of the perivascular spaces. In the presence of an obvious fistula one can hardly see the need of such an extensive and radical procedure, fraught with such possibilities just mentioned. Eagleton³³ skeletonizes the posterior aspect of the petrous bone by the removal of the sinus plate, the tegmen, the bone over Trautmann's triangle and then removes the root and some of the zygoma, the squama and some of the anterior canal wall, thus skeletonizing the anterior portion of the petrosa. The tegmen is then completely removed and the dura elevated, bringing the petrous tip into view, which is entered by removing the bone overlying the apex. Almour¹ has developed a logical technical approach that is especially indicated for drainage of an empyema of the tip in a pneumatisized petrous pyramid in which no demonstrable fistula is evident. Following a radical mastoid operation the tensor tympani muscle is removed and the orifice of the Eustachian tube identified. Then by means of a drill a tract is made by placing the burr point in the roof of the mouth of the Eustachian tube and burring inward and forward at an angle of 22 degrees to the external canal. This technique in forming a tract along the peritubal cells gives adequate, dependent drainage to the tip. Further, it seems to follow the path that has been so frequently described in many cases in which a spontaneous fistula has been affected by Nature. It is obvious that any of these techniques may not be necessary as a rule in cases in which at the time of operation a fistula had been found either in the epitympanum or in the middle ear. In such instances, probably all that is necessary is the widening and curettement of the established tract so as to afford efficient drainage. Lillie³⁴ has reported 2 such cases in which cures were effected by widening and curettement of a fistula that appeared in the epitympanum, and Seydell³⁵ reports similar success in the use of this procedure.

Myerson, Rubin and Gilbert³⁶ advocate entry into the anterior wall of the petrous tip by means of a special gouge, after the performance of a thorough simple mastoid operation. They claim that their procedure effects a thorough evacuation of the petrous tip with preservation of the patient's hearing. In another contribution³⁷ on the subject they point out the frequent bottle-neck arrangement of the fistula which they believe would at times preclude efficient drainage and therefore advocate uncappping of the anterior wall of the pyramid.

A review of the recorded cases makes it obvious that no one of the procedures described is equally applicable in all cases. It would appear logical to perform first an extensive and thorough simple mastoid operation and then search for the presence of a fistula at the sites of predilection: either anterior or posterior to the superior semicircular canal,

either within or above the arch of the superior semicircular canal, and either below or posterior to the posterior canal. If a fistula be found at any of these sites it might be widened and enlarged and the patient carefully observed. If the postoperative progress was unsatisfactory, then the petrosa might be entered and the tip uncapped. If, however, no fistula is found, the simple mastoid cavity might be converted into a radical mastoid cavity and search made for a fistula either at the Eustachian tube orifice or just above it. A fistula found in this region is treated by enlarging and widening its tract and careful postoperative observation will decide as to the adequacy. If no fistula is found at this time, then recourse to a more radical procedure is necessary. Here one may have his choice of those suggested by Almour, Eagleton, or Myerson and his associates.

The exact indication for surgical intervention on the petrous pyramid has not as yet been definitely determined and a great deal of confusion still exists.

Certainly not all cases of petrosal involvement require surgery. It is conceivable that the petrous tip may be but mildly involved in the pathologic process and it has probably been the experience of most otologists that many of their cases of mastoiditis with pain in and about the eye have gotten well without a petrous operation. In fact, Myerson³⁶ states that about 80% may recover with conservative management. Yet the potential complications of meningitis, brain abscess, cavernous sinus thrombosis and general sepsis are of such a grave and frequently fatal nature as to make us profoundly conscious of our responsibility when confronted by a case of petrosal infection. While no hard and fast rule may be drawn, conservative management seems to be indicated only in those cases in which the pain is mild and decreasing in intensity, in which the temperature is normal, or slightly elevated, in which the discharge has not abruptly ceased and in which the Roentgen ray findings show either a normal or a slightly involved petrous tip. On the other hand, pain increasing in intensity, especially if it be nocturnal and interfere with sleep, a rising temperature, a sudden cessation of the discharge, positive Roentgen ray findings, and signs of sepsis or meningeal irritation all point to an immediate evacuation of the petrous tip as a means of preventing further progression of the purulent process towards the cranial cavity with the possible production of a fatal complication. The danger lies, not in the operation, but in the delay during which meningitis, brain abscess or cavernous thrombosis may supervene.

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- (Titles have been omitted for sake of brevity.)

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 21, 1935.

The Water of Serum and the Calculation of the Molality of a Solute in Serum From the Measurement of the Specific Gravity.—FREDERICK WILLIAM SUNDERMAN (John Herr Musser Department of Research Medicine, University of Pennsylvania). Recent studies have demonstrated the desirability in certain instances of expressing the concentration of a solute in serum in relation to the concentration of water. For this relationship the measurements of both the specific gravity and the amount of total solids have been necessary. A linear correlation has been demonstrated between the specific gravity and the total solids of serum so that having determined either of these two measurements a solute measured in relation to volume may be calculated in relation to the water within an accuracy of $\pm 1\%$. In addition the concentration of the water or of the total solids present in serum may be derived directly from the measurement of the specific gravity.

The Fate of Hemoglobin Injected Into the Blood Stream.—DAVID L. DRABKIN, A. H. WIDERMANN and H. LANDOW (Laboratory of Physiological Chemistry, University of Pennsylvania). Small samples of hemolyzed, washed blood cells, containing 0.1 to 0.4 mM. of hemoglobin, were injected intravenously into the same dogs from which the blood was obtained. The fate of the injected blood pigment was followed during the first 20 hours by periodic examination of the serum and of the urine.

By means of spectrophotometric analysis the following points were established: (1) The pigment which appeared in the urine was unchanged hemoglobin. (2) Upon standing, the hemoglobin in the urine was converted rapidly into methemoglobin. This change was due most probably to the presence of oxidants in the urine. (3) In most of the experiments the hemoglobin which appeared in the urine accounted for only one-tenth of the quantity which disappeared from the serum. (4) During the first 20 minutes after the injection, 20 to 45% of the injected pigment was removed from the serum. There appeared to be an inverse relationship between the magnitude of the early loss from the serum and the total hemoglobin which was excreted in the urine. (5) Within 8 hours after injection 90% of the hemoglobin had disappeared from the serum. When HbO_2 was injected neither methemoglobin nor bile pigments could be demonstrated in the serum during the course of the experiments. (6) Injected methemoglobin disappeared from serum at the same rate as injected HbO_2 . Some evidence of alteration in pigment, perhaps to a hematin-like substance, was obtained after the injection of methemoglobin. (7) Splenectomy produced no demonstrable effect upon the rate of removal from serum of injected HbO_2 .

The Absorption of Cystin, Methionin and Cysteic Acid From Intestinal Loops of Dogs.—JAMES C. ANDREWS, CHARLES G. JOHNSTON and KATHLEEN C. ANDREWS (Laboratories of Physiological Chemistry and Research Surgery, University of Pennsylvania). The relative rates of absorption of cystin, methionin and cysteic acid have been measured in a dog with an isolated intestinal loop with the result that methionin appears to be absorbed about three times as rapidly as cystin, while the rate of absorption of cysteic acid is intermediate between the two. Since the dog employed for these experiments is the same one which was used over 2 years ago in measuring the rates of absorption of cystin and cysteic acid, we have been able to determine the change in the rates of absorption of these two compounds over that length of time. We found that for both compounds the rate of absorption has decreased to about one-third its original value. The rate of absorption is not a linear relation. In a 6-hour experiment the amount of cystin absorbed is two or more times as great as in a 4-hour experiment. The amount of the amino acid absorbed in a given length of time varies somewhat with the amount placed in the loop: the larger the dose the more is absorbed. The amount of the amino acid absorbed is independent of whether it is administered as the free ampholyte or as the sodium salt.

The amount of the base absorbed from the salt is sufficiently specific and independent of the amino acid with which it is combined as to suggest that its absorption is an independent process when the salt is

capable of hydrolysis (cystin and methionin) but is not independent in the case of the sodium salt of cysteic acid where the salt is incapable of hydrolysis. In this latter case the salt appears to be absorbed as such in equimolar amounts of base and acid.

The Effect of Intense Sound Waves on Some Biologically Important Chemical Reactions.—LESLIE A. CHAMBERS (Johnson Foundation for Medical Physics and the Department of Pediatrics, University of Pennsylvania). The most characteristic manifestations of the action of sound on living cells are loss of motility, plasmolysis, vacuolation and disintegration in the order stated. While the lethal action is most pronounced in the presence of cavitation, it also proceeds under pressures which inhibit the formation of cavities in the supporting medium.

In order to explain the biologic action the response of certain simple chemical systems to vibration has been studied. Among the reactions accelerated or induced by audible sound are oxidation of halides, oxidation of H_2O , hydrolyses, depolymerizations and protein denaturation. No reaction has been found to be affected in absence of cavitation.

Protein denaturation by sound requires the presence of certain specific dissolved gases and does not occur in the presence of certain others. Therefore the reaction may not be attributed to kinetic energy increments due to local degradation of acoustic energy.

Furthermore, the specificity of the denaturation reaction toward certain gases indicates a type of energy transfer quite unusual. The unexpectedness of the energy relationships is still further emphasized by the fact that light is emitted from pure water and other liquids during intense vibration.

Complete explanation of the biologic action of sound must await knowledge of these unorthodox energy transfers. However, the observations indicate that intense acoustic fields may be of great value as an experimental tool in both physical and physiological chemistry.

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